Harms of Antiepileptic Drugs: Issues in Reporting and Systematic Reviews

by

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Abstract

Aims

In this thesis, we shall discus the reporting of harms in randomised controlled trials using the CONSORT statement for harms 2004. To determine if reporting has changed since the introduction of this standard.

To evaluate the effects of lacosamide when used as an add-on for drug resistant epilepsy in a systematic review and use it as a model to test hypothesis if harms.

Develop new tools and methodologies in analysing harms in systematic reviews and to test of harms across indications can be used for antiepileptic drugs in systematic reviews

Methods

Statistical analyses were conducted using SPSS version 17, RevMan version 5.0 and Comprehensive Meta-analysis version 3.0 to analyses data.

Continuous variables were compared with means using the Student t-tests analyses of variance (ANOVA). Proportion data were compared using relative risks. These were calculated using either and random or fixed effects models where appropriate.

Heterogeneity was explored using statistical tests of heterogeneity and meta-regression.

One hundred and fifty two RCTs published between 1999 and 2008 were included for analysis. Three epilepsy RCTs published between 2007 and 2010 were include for systematic reviews of lacosamide and an additional four neuropathy trials were included. One hundred and six randomised controlled trials of antiepileptic drugs were included to analyses harms across indications.

Results

We identified 23 criteria in the CONSORT statements. The mean number of criteria met per trial was 11.3 (95%CI 10.6—12.0). Commercially funded studies met 12.6 and non-commercially funded met 9.4 ($p < 0.001$). Trials recruiting adults met 12.5 and trials recruiting children met 9.3 ($p < 0.001$). Trials published before 2004 met 11.6 and trials published after 2004 met 11.1 ($p = 0.53$). Commercially funded trials met the majority of criteria more than non-commercially sponsored trials, particularly for definition of AEs (RR 3.15, CI 1.67—5.95) and the use of a validated dictionary of terms (RR 3.46, CI 1.41—8.44). Definitions for AEs (RR 2.32, CI 1.07—5.02) and details of analyses (RR 2.05, CI 1.01—4.15) were reported in adult trials more often than trials in children.

Three lacosamide trials were included in systematic reviews. The overall risk ratio for a 50% or greater reduction in seizure frequency for all doses of lacosamide compared to placebo was 1.70 (CI 1.38 to 2.10). The overall risk ratio for seizure freedom for all doses of lacosamide compared to placebo was 2.50 (CI 0.85 to 7.34). The overall risk ratio for treatment withdrawal for all doses of lacosamide compared to placebo was 1.88 (CI 1.40 to 2.52). Adverse effects, which were significantly associated with lacosamide, were abnormal coordination, blurred vision, diplopia, dizziness, fatigue, nausea and vomiting.

Four lacosamide trials of neuropathy were selected and harms data form these were incorporated to data from epilepsy trials. The following harms outcomes: Any adverse events, dizziness, fatigue, headache, nasophryngitis, nausea, somnolence, tremor, vertigo, vision blurred, vomiting and withdraws due to adverse events were meta-analyzed. Only tremor (I^2 of 0-64%) and nasophryngitis (I^2 of 27-64%) showed significant heterogeneity in statistical tests. only outcome that changed effect size to

yield a significant result when neuropathy trials were combined was fatigue. For the 400mg dose of lacosamide, the summary measures were 2.0 (95% CI of 1.0 to 4.03) and this changed to 1.98 (95% CI of 1.11 to 3.52) when neuropathy trials were combined. Therefore, harms across indications could be used for lacosamide.

To test the hypothesis if harms across indications such as headache and neuropathy trials of other antiseptic drugs, meta-regression was used to further explore heterogeneity. Only lacosamide and lamotrigine could have harms across indications summated in systematic reviews but not for pregabalin and gabapentin due to significant heterogeneity, which could be explained by dose effects.

Conclusion

Reporting of AEs in RCTs of AEDs is poor and has not improved since the publication of the CONSORT guidelines on the reporting of harms. Commercially funded trials were better reported than non-commercially funded trials and trials recruiting adults were better reported than trials recruiting children. These findings have serious implications as poor reporting precludes bias being detected and hinders adequate risk benefit analyses. Journal editors, authors and reviewers should be encouraged to follow current guidance.

Lacosamide is effective in treating partial epilepsy versus placebo for the 200mg, 400mg and 600mg doses. Harms from neuropathy trials can be used to improve harms reporting in systematic reviews of lacosamide. Harms across indications could also be used for lamotrigine but not for pregabalin and gabapentin. Novel methods need to be developed for incorporating observational studies in systemic reviews.

Clinicians and Journal Editors need to have a greater awareness of poor harms reporting in RCTs and this needs to be more transparent.

Outline of thesis chapters

This thesis explored the reporting of harms in randomised controlled trials and provides recommendations for reporting of harms in trials and systematic reviews.

This work has provided novel insights into how harms caused by antiepileptic drugs are reported in randomised controlled trials. We suggest ways in which the reporting of harms can be improved in randomised controlled trials. A systematic review of lacosamide provided novel insights on how harms are analysed in systematic reviews. This model was used to explore ways in which analyses of harms in systematic reviews can be improved with suggestions for further work.

Chapter 1- Defines epilepsy and seizures and how epilepsy is diagnosed. Common antiepileptic drugs are discussed and studies of risk of seizure recurrence after a first and second seizure. This is illustrated in the MESS study and how this adds to how one manages patients with a first unprovoked seizure.

Chapter 2- Discusses clinical trials and evidence based medicine with descriptions of common clinical trials. Findings from the SANAD studies are discussed, regarding the best treatment for focal and generalised epilepsy.

Chapter 3- Discusses harms of antiepileptic drugs, the definition of harms and how harms are analysed in randomised controlled trials. Describes the recent developments in classification of harms, and recent quality of life measures used in a clinical setting to record and elicit adverse events like the Liverpool Adverse Event Profile (LEAP). Discusses a recent case comparison study of these tools in patients newly diagnosed in epilepsy.

Chapter 4- Discusses the CONSORT statements. Describes the history of the CONSORT group and describe the CONSORT statements and the extensions of the CONSORT statements. Reviews a number of studies that have used the CONSORT guidelines as a benchmarking tool. Results from these studies were analysed narratively.

Chapter 5- Discusses the rationale behind systematic reviews, meta-analyses and meta-regression methods. Some of these methods I will use in this thesis.

Chapter 6- This chapter discusses the reporting of harms in randomised controlled trials of antiepileptic drugs. They will discuss the methods used in analysing trials and describe the reporting of harms using the CONSORT statement. Factors such as type of journal source of funding and publication date as possible predictors on the quality of harms reporting are explored.

Chapter 7- In this chapter I discuss the use of lacosamide and its used as an antiepileptic drug. I describe a systematic review of lacosamide as add-on therapy in partial epilepsy. The results of this review may be further evaluated in the next chapter will be describe harms across indications for lacosamide.

Chapter 8- Here, I will discuss lacosamide as an example of how harms across indications can be better analysed. My aims are to determine if estimates of effect sizes increase in proportion to dose increases. The presence of significant heterogeneity would imply that harms across indications, cannot be used. I used meta-analyses software to make judgements.

Chapter 9 –Discusses if harms data across indications of other AEDs can be meta-analysed. I hypothesised that harms across indications cannot be used for AEDs other than lacosamide I used both meta-analysis and meta-regression methods to explore heterogeneity and used outputs from these to accept or reject the null hypothesis.

Chapter 10- A discussion of major finding of my work, and recommendation for improving he reporting of harms.

Authors Declaration

This thesis is the result of my own work. The material in the thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or qualification.

The research was carried out in the Epilepsy Research Group, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool.

Most of the work is mine, however some of it is collaborative. I am particularly indebted to Prof Anthony Marson (Professor of Neurology, University of Liverpool) and Dr Catrin Tudur-Smith (Reader in Biostatistics, University of Liverpool) and for their guidance and support and their assistance in interpretation of statistical analyses presented in chapter seven and eight. I am also grateful for Dr Graham Powell (Academic Clinical Fellow Walton Centre NHS) who assisted me in selecting trials for inclusion in chapter 7. I am also grateful to Mr Andrew McKay (Biostatistician in Institute of translational medicine) for his assistance in selecting trials and being part author of the lacosamide review presented in chapter eight.

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This thesis is dedicated to my late father Mr Ali Mohammed Shukralla Al Emadi.

Abbreviations

ACTH	Adrenocorticotropic Hormone
AED	Antiepileptic Drug
AAN	American Academy of Neurology
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
CRB	Carbamazepine
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	Gabapentin
HLA	Human Leucocyte Antigen
ILAE	International League Against Epilepsy
LEV	Levetiracetam
LTG	Lamotrigine
LCS	Lacosamide
OXY	Oxcarbazepine
PGABA	Pregabalin
PHY	Phenytoin
RCM	Racemide
RCT	Randomised Controlled Trial
RTG	Retigabine
RUF	Rufinamide
SANAD	Standard And New Antiepileptic Drugs
SUDEP	Sudden Unexpected Death in Epilepsy
TIG	Tiagabine
TOP	Topiramate
VAL	Valproate
VIG	Vigabatrin
ZNS	Zonisamide

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Chapter 1

What is epilepsy and how are seizures treated?

1.1 What is epilepsy?

The word epilepsy comes from the Greek word επιαμβανεν, which means 'being seized' or overwhelmed by surprise (Temkin 1945). Epilepsy and seizures are well described in the Hammurabi code dated 1780 B.C. The texts describe seizures in great detail and they were thought to be punishments for sin. This negative view of epilepsy remained until the nineteenth century when Jackson hypothesised that seizures are due to alterations in neuronal function. Since then an organic basis of epilepsy has been increasingly recognised and consequently treatment methods changed.

Seizures are the physical manifestation of epilepsy, but patients commonly suffer social isolation, depression and adverse events due to medications. Other implications of epilepsy include higher rates of unemployment, inability to drive and implications on human reproduction (Shovron et al 2011).

To meet a diagnosis of epilepsy by convention, a patient must have had at least two unprovoked seizures. Seizures are defined as brief sudden attacks with alteration of consciousness with motor, sensory, cognitive, psychic or autonomic disturbances caused by abnormal excessive or synchronous neuronal activity in the brain (Fisher et al 2005). Reaching a definition for a heterogeneous condition like epilepsy has been difficult. The International League Against Epilepsy (ILEA) formulated a definition of epilepsy as:

> "..a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of the condition" (Fisher et al 2005).

The diagnosis of epilepsy can be made with a minimum of one seizure and provoked seizures are not included unless the provocation is enduring like a tumour. To resolve issues that arise with symptomatic epilepsy a new operational definition of epilepsy has been proposed:

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

These definitions of epilepsy and seizures are useful guidelines but the clinical diagnosis of epilepsy is fraught with challenges.

1.2 **How are seizures and epilepsies classified?**

Seizures can be broadly classified as partial seizures, generalised seizures or unclassified seizures. Individual classification of seizures can be very simple as shown in table 1

Seizure classification
I Focal Seizures
A Simple partial seizures
B Complex partial seizures
II Generalised seizures
A Absence seizures
B Atypical absence seizures
C Tonic-clonic seizures
D Myoclonic seizures
E Tonic seizures
F Clonic seizures
G Atonic seizures
III Unclassified seizures

Table 1 Classification of Seizures.

Partial seizures are due to a focal abnormally in the brain that may or may not spread to other areas of the brain. These can be simple partial seizures where there is no alteration of consciousness or complex partial seizures where an alternation of consciousness occurs.

Generalised seizures are those that have no identifiable onset like simple partial or complex partial seizures. They affect both sides of the brain simultaneously. Generalised seizures can be composed of absence seizures where patients have a sudden behavioural arrest, which typically lasts up to 30 seconds.

Tonic-clonic seizures are well known to the layman as grand-mal seizures. Here there is an abrupt loss of consciousness followed by a tonic contraction of muscles, which result in an exhalation of air followed by upward eye deviation. This is followed by flexion of the elbows of the upper extremities and extension of the lower extremities. These seizures can arise either independently or they can arise from spread of simple partial or complex partial seizures. The identification of a focal seizure or one that has a focal onset is important as this may have implications for surgical removal of the epileptic zone. Figure 1 further outline seizure classification.

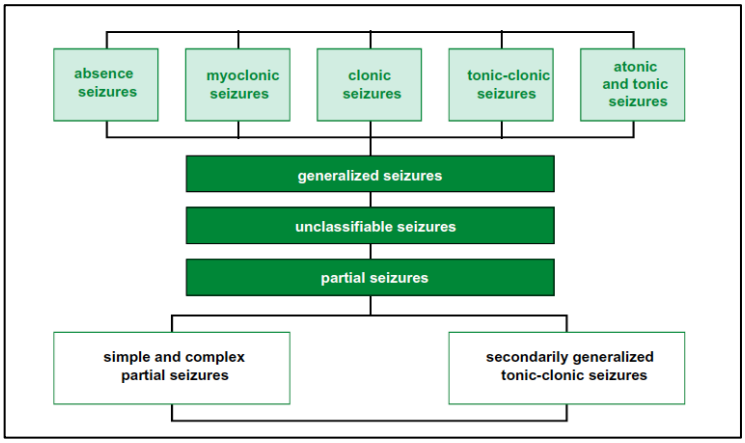


Figure 1 International classification of seizures: Adopted from Schmidt & Elger 2008.

Merlis attempted the first classification of the epilepsies in 1970 as shown in table 2 page 5 (Merlis 1970). This classification was simple with three main axes. This classification was simple and was based on the semiology of seizures.

I.	Generalised epilepsies a. Primary generalised epilepsies b. Secondary generalised epilepsies c. Undetermined generalised epilepsies
II.	Partial epilepsies
III.	Unclassified epilepsy.

Table 2 Classification of epilepsy proposed by Merlis 1970.

This classification was difficult to use as secondary generalised seizures were confused with secondary generalised epilepsy. Moreover, the classification was dependent on EEG characteristics of the patient. As more epilepsy conditions were discovered then the classification had to be revised. Subsequent revisions of the classification of seizures and epilepsies occurred in 1981 and 1989, but this was reviewed in 2001 (Bancaud et al 1981) (ILAE 1989).

Engel proposed a revision to the earlier classification and proposed that an elaboration by adding other dimensions to the simplistic classification. He proposed five axes, which could be considered when making a diagnosis (table 3 page 6). Firstly, the history and phenomenology of seizures should be obtained from patients. Secondly the seizures should be classified based on semiology and thirdly the epilepsy syndrome should be classified along with the aetiology of epilepsy if possible. A final attempt, although optional is the classification of the degree of impairment (Engel 2001).

Some changes in the terms used have occurred to reflect a pragmatic approach to epilepsy classification. The terms idiopathic, symptomatic and cryptogenic have been replaced with genetic, metabolic/structural and unknown. Further changes to seizure classification included a replacement of the term simple partial to focal sensory or focal motor seizure; and complex partial seizures to focal dyscognitive seizures (Berg et al 2010).

Diagnostic scheme of Epilepsy based on five Axes	
Axis 1	Ictal phenomenology, from the Glossary of Descriptive Ictal Terminology, can be used to describe ictal events with any degree of detail needed.
Axis 2	Seizure types, from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
Axis 3	Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndrome based diagnosis may not always be possible.
Axis 4	Aetiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
Axis 5	Impairment or disability caused by epilepsy. This can be optional, but often useful. Additional diagnostic parameters can be derived from an impairment classification adapted from the WHO ICIDH-2.

Table 3 Diagnostic Scheme of the Epilepsies by Engel 2001.

1.3 **Epidemiology of epilepsy**

Four hundred and fifty million people suffer from neurologic or psychiatric disease globally. The proportion of these with epilepsies is estimated to be 50 million. The World Health Organisation, the International League Against Epilepsy (ILAE) and the international bureau for epilepsy have in partnership published a report whose aim was to bring epilepsy 'Out of the Shadows' (WHO 2003). Several studies have calculated the rates of incidence and prevalence. Incidence is expressed as the number of new cases of disease in a population per unit of time. Commonly this is given as the number of cases per 100 000 of population per year. Prevalence is the total number of persons with the disease at a specific moment of time. This is expressed as per 1000 population.

The lifetime prevalence of epilepsy is 5-8 per 1000 in high-income countries; the prevalence of epilepsy in the UK according to 2005 figures is 9.5 per 1000. The point prevalence of epilepsy is the proportion of a given population having epilepsy at a given time. This is estimated to be 0.4 to 0.8% in Europe (Sander & Shovron 1996). About 1% of the population have active epilepsy at any given point in time.

Incidence of epilepsy on the other hand varies with age. The age specific incidence rate of non-febrile seizures is high in childhood and declines between ages of twenty to fifty followed by an increase after the age of fifty. The Rochester Minnesota registry estimates that the age-adjusted incidence of epilepsy was 44 per 100,000 person-years.

The most common antecedent to seizures was stroke in 11% of patients. The cumulative incidence of epilepsy up to 74 years is 3.1% (Hauser et al 1993).

Epilepsy is associated with an increased mortality. It is estimated that the mortality of epilepsy is 2-3 times greater than that of the general population (Lhatoo et al 2001). Causes of death from epilepsy ranges from deaths due to underlying disease, deaths due to seizures due to status epilepticus, drowning and trauma. Deaths can occur due to sudden unexpected death in epilepsy (SUDEP). Also, deaths can occur due to surgical and medical treatments of epilepsy due to adverse events. The magnitude of deaths due to SUDEP has been well described and this is the commonest cause of death in epilepsy (Smithson et al 2014). Population based studies suggest that the incidence of SUDEP is between 0.09 to 2.31 per 1000 patient years (Smithson et al 2014).

Deaths can also occur due to harm of antiepileptic drugs, the incidence of these is not fully described. Other deaths can occur due to suicide in epilepsy and this too can have varying causes. Epilepsy is still a disease that is associated with considerable stigma for patients and this is due to the pervasiveness of negative perception of the disease (Baxendale & O'Toole 2007).

1.4 Natural history of untreated and treated epilepsy

Kwan and Brodie were the first to prospectively determine the natural history of treated epilepsy (Kwan & Brodie 2000). Sixty three percent of patients were seizure free after the first AED. In their study, they found that 47% of untreated patients became sire free after the first AED and 14% became seizure free after the second drug. Questions therefore arise on the natural history of untreated epilepsy.

1.4.1 Natural history of untreated epilepsy

A discussion of untreated epilepsy has many aspects to consider. First is the risk of seizures after a first seizure, this then followed to the risk of seizures after second and third seizure. Once one has considered this, then the next logical question is if patients after a first seizure should be treated or not. These issues will now be discussed in turn.

If a patient has had two seizures, then there is little debate that antiepileptic drugs are indicated. However, if only one seizure has occurred then there is significant debate on the need to commence AEDs. Earlier studies have shown that only 30% of patients will have seizures in 3 years (Hauser 1982) as shown in the figure below (figure 2). Pooled estimates from other studies show that the risk of seizure recurrence increases as time goes by but this is greatest in the first year (fig 3) (Krumholz et al 2015). Other studies have quoted proportions from 23% to 71%. A qualitative review by Berg and Shinar summated Kaplan Meir survival estimates from various studies (Berg & Shinnar 1991). They included sixteen studies with a mixture of methods used to ascertain the risk estimates. However, they used data from 13 studies to calculate an estimate. Their results showed that the 2-year recurrence risk was 46% (95% CI of 44-49%). A consistent trend was seen across the studies where abnormal electroencephalogram (EEG) and seizure aetiology were strong predictors of seizure recurrence.

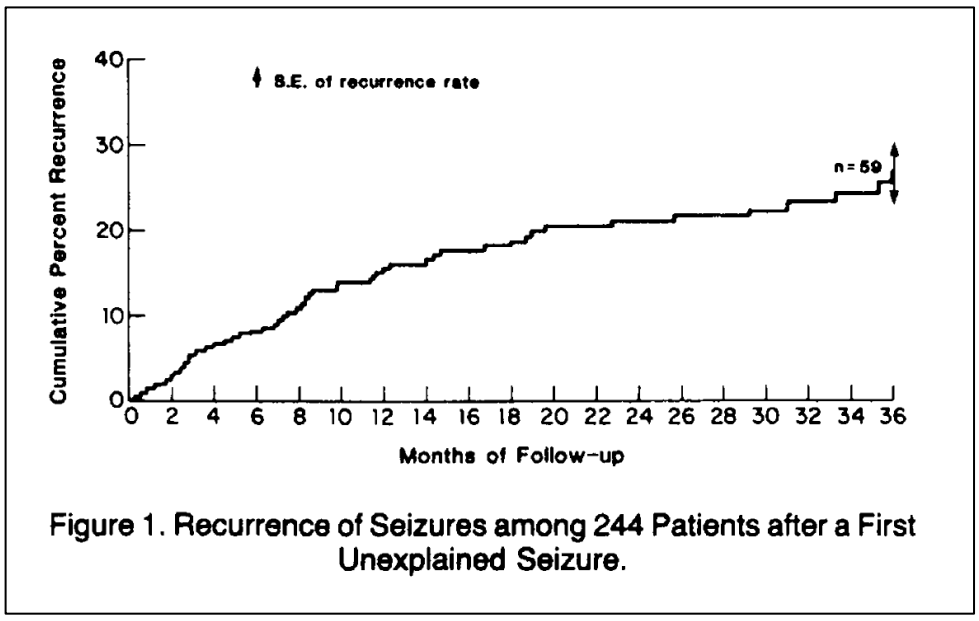


Figure 2 Cumulative percentage risk of seizure at three years after first seizure: Adopted from Hauser et al 1981.

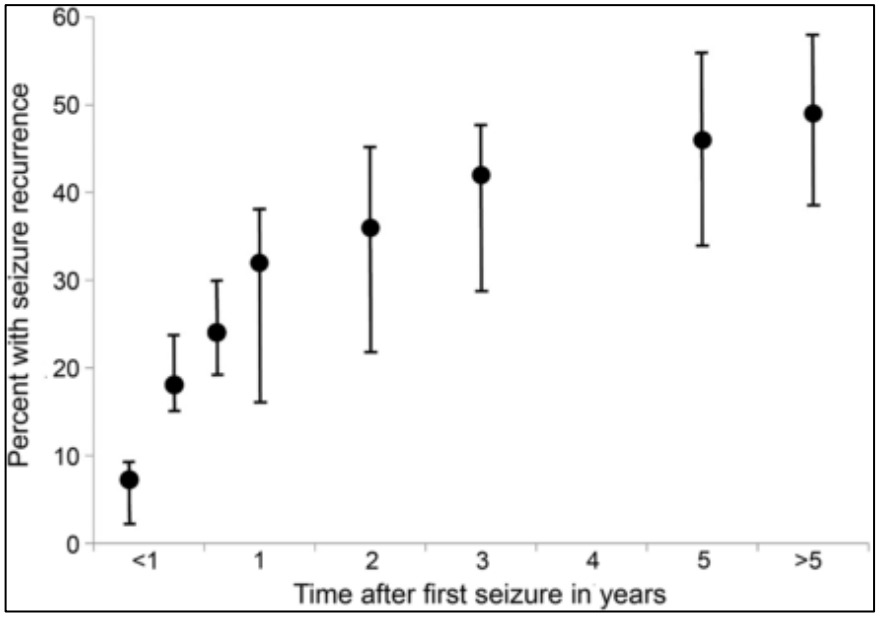


Figure 3 Percentage of patients with first seizure experiencing a recurrent seizure over time showing the cumulative risks from twelve studies: Adopted from Krumholz et al 2015.

There have been three other studies that have looked into the treatments of first seizures. These include the FIRST study followed by the MESS study.

The FIRST study was a multicentre Italian study that reported the risk of recurrent seizure after an untreated or treated first unprovoked seizure (FIR.S.T group 1993). This trial evaluated the risk of having a subsequent seizure after having a first unprovoked seizure that was not treated and compared this to a treated group. The risk of recurrence was 18% at 3 months, 28% at 6 months and 41% at 12 months. The risk of seizure at 24 months was 51%. This study also showed that having an abnormal neurologic exam was not associated with an increased risk of relapse (HR 0.8 95% CI of 0.4-1.6). Also, there was no increased risk of relapse if there were abnormalities on EEG. Compared to the MESS study the FIRST study recruited 204 patients in the treated arm and 193 patients in the untreated arm. Therefore, this was a comparatively smaller study and could explain why the hazard ratios were not significant in many of the covariates studied (figure 4 page 10).

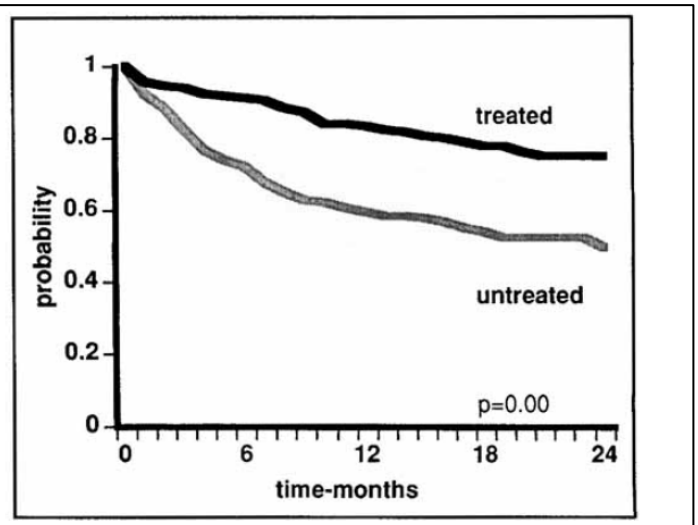


Figure. Cumulative probability of remaining seizure-free by treatment, all subjects.

Figure 4 Probability of remaining seizure free by treatment allocated: Adopted from the FIR.S.T study 1993

1.4.2 The MESS study and the natural history of untreated epilepsy

The earlier studies examined the risk of recurrence of seizures after a first seizure. The MESS study sought the answer the question on the risk of seizures if patients are started on treatment early or if treatment is deferred. This was a multicentre open labelled study (Marson et al 2005).

Patients that were suitable for the MESS study included those patients where both the clinician and the patient were in a state of clinical equipoise regarding initiation of treatment. Patients were allocated to either deferred or immediate treatment with AEDs. The primary outcomes were:

1. Time from randomisation to first seizure of any type
2. Time from randomisation to first tonic clonic seizure
3. Time from randomisation to the second and fifth seizures
4. Time from randomisation to 2-year remission of seizures
5. Proportion of patients who were seizure free for 2 years between 1 and 3 years after randomisation and between 3 and 5 years after randomisation.

Immediate treatment increased time to first seizure compared with deferred treatment with a hazard ratio of 1.4 (95% CI of 1.2 to 1.7) and to second seizure hazard ratio of 1.3 (95% CI of 1.1 to 1.6). For patients with a single seizure, the risk of relapse is 32% for immediate treatment and 39% for deferred treatment. This risk difference after five years to is 42% for immediate treatment and 51% for deferred treatment. Although immediate therapy had a beneficial effect this effect was lost at 4 years (Marson et al 2005). This data is shown in the Kaplan Meir plot below (figure 5).

The actuarial estimate of achieving a 2-year remission was different too in the treatment groups with a 69% of patients entering remission in the immediate treatment group and 61% of patients in the deferred treatment group for single seizures.

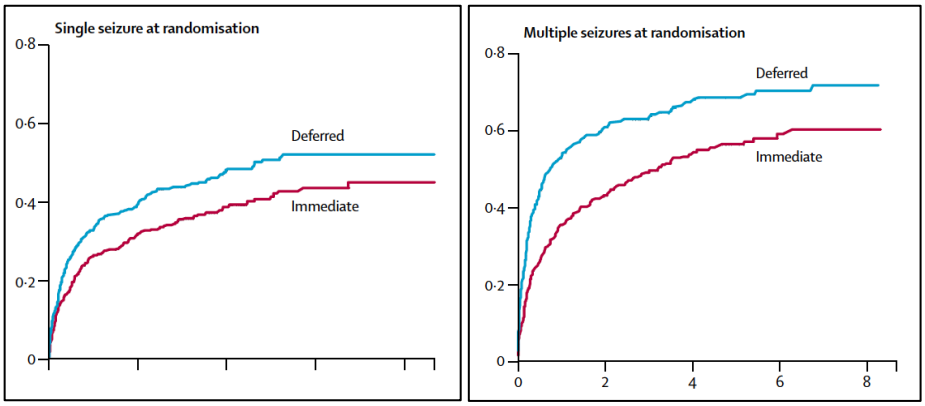


Figure 5 Cumulative probabilities of seizures versus years since randomisation: Adopted from Marson et al 2007.

Further to the initial report of the MESS study, prognostic tools were developed to predict the risk of seizures into low, medium and high risk (Kim et al 2006). The model developed factors to predict the risk of seizures. Low-risk patients were those that had a single seizure, with no neurologic deficit and a normal EEG. Medium-risk patients are those with 2-3 seizures or no neurologic deficit or an abnormal EEG. High-risk patients were those with four or more seizures with or without neurologic deficit and or an abnormal EEG

Overall the results of the MESS study were in agreement with other studies in that seizures beget seizures and repeated seizures have a negative impact on the central nervous system homeostasis. The experimental evidence from rat models doesn't

support this view (Sills 2007). However, the MESS study also shows that deferred treatment of patients that are in low risk is no different to patients that have immediate treatment. The implication of this is that some patients can be deferred treatment with AED as this may prevent patients being exposed to adverse events.

A study by Hauser et al evaluated the risk of seizures after a second seizure. They calculated the risk of a second seizure after a first seizure was 33%. The risk of a third seizure after a second seizure was 32% at 3 months, 41% at six months, 57% after one year and 73% after four years (Hauser et al 1998) (fig 6). The risk of a third seizure after the second seizure was greater in patients with remote symptomatic epilepsies (87% at five years) versus idiopathic (64% at five years) (fig 7 page 13).

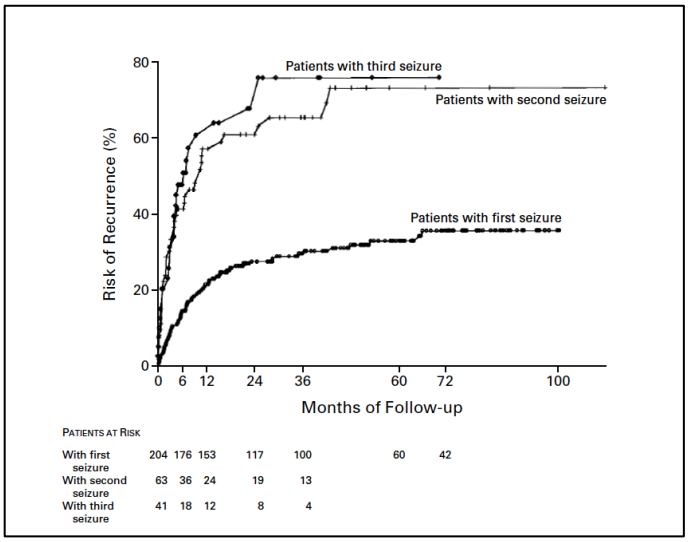


Figure 6 Risk of second, third and fourth unprovoked seizure after a first, second and third unprovoked seizure: Adopted from Hauser et al 1998.

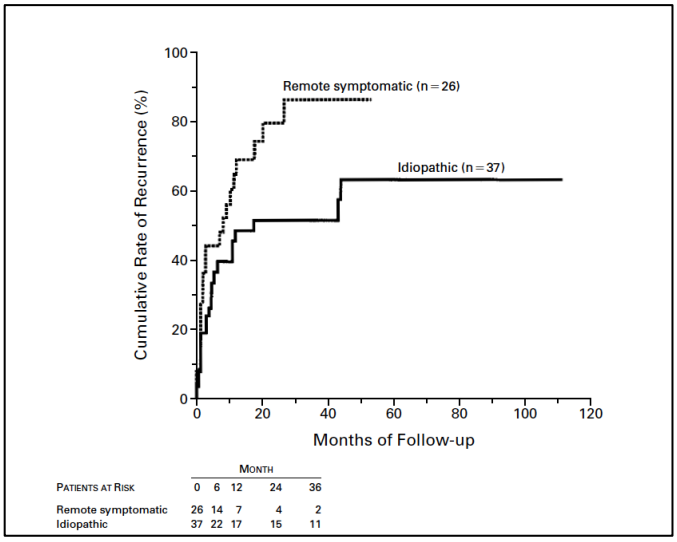


Figure 7 Risk of third unprovoked seizure after a second unprovoked seizure in patients with remote symptomatic and idiopathic epilepsy: Adopted from Hauser et al 1998.

Including the FIRST study and the MESS studies there are four other trials that compared the risk of seizure after first unprovoked seizures. All studies compared the risk in treated and untreated patients. The largest of these is the MESS study followed by the FIRST study. A summary of the findings are shown below where it is clear that there is significant heterogeneity between the studies and this was confirmed by a narrative review of this data (Sathasivam & Nicolson 2008) (fig 8). A further systematic review of the risk of seizure reduction after treatment of the first seizure by Wiebe et al found that the absolute risk reduction of seizures 34% (95% CI 15-52) when six trials are meta-analysed (Wiebe et al 2008) (fig 9 page 14).

Study	**Seizures**	**Seizure recurrence treated**	**Seizure recurrence untreated**	**Difference (untreated minus treated)**
Camfield et al	GTCS, SGTC, CPS.	14.3 %	52.9%	38.6%
Chandra	GTCS, SGTC, CPS.	4.3%	55.7%	51.4%
FIR.S.T	GTCS, SGTC	18%	39%	21%
Gilad et al	GTCS.	22%	71%	49%
Das et al	GS	11.1	45%	33.9%
Marson et al	GTCS, SGTC, CPS, M, A.	18% at 6 months 46% at 8yrs	26% at 6 months 52% at 8 yrs	8% at 6 months 6% at 8 years

Figure 8 Randomised trials of treatment of patients with single unprovoked seizures: Adopted from Sathiasivam & Nicholson 2008. GTCS -generalised tonic clonic seizures, SGTC- secondary generalised tonic clonic seizures, CPS -complex partial seizures, GS- generalised seizures, M- myoclonic seizures, A- absence seizures.

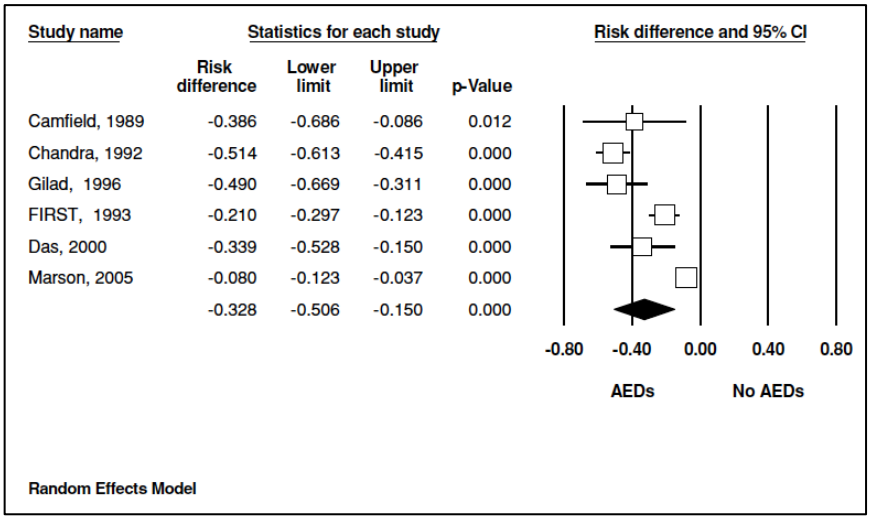


Figure 9 Meta-analysis of randomised trials of treatment of AEDs versus no treatment in patients with first unprovoked seizure: adopted from Wiebe et al 2008.

1.4.3 Response of treated epilepsy

Several studies including the MESS studies have elaborated on the risk of seizures after the first or second seizure. However, patients also ask about the likelihood they will become seizure free after treatments and the probability of treatment response.

Patients who are prescribed antiepileptic drugs for the first time respond very well (Brodie et al 2009). Approximately 50% of patients will be seizure free after the first drug and this will occur at a modest dose. This response decreases with subsequent AEDs, see table 4 page 15. The authors compared seizure freedom rates for monotherapy and polytherapy regimens (Brodie et al 2009) see table four below. A total of 1098 patients were enrolled in their study. Of the patients included, 49.4% were seizure free after the first AED. This was reduced to 36% after a second drug and then 25% of the third drug and 16% on the fourth drug.

Epilepsy treatment response can therefore be thought of three groups, each in a state of flux. The first is the responsive group comprises 50% of patients. The second group consists of about 20% of patients and these will reach seizure remission after a further AED. Finally, the third group that do not remit and continue to have seizures despite multiple AEDs, this comprises about 20% of patients, see figure 10 page 15.

Newly Diagnosed Epilepsy. Seizure freedom rates (%) according to regimen				
	N	One AED	Multiple AEDs	Total
First AED	1098	49.4	0	49.4
Second Regimens	398	25.4	11.3	36.7
Third Regimen	168	15.5	8.9	24.4
Fourth regimens	68	8.8	7.4	16.2
Subsequent regimens	46	6.5	10.8	17.3
AED regimens were selected according to clinical practice				

Table 4 Seizure freedom according the AED regime: Adopted from Brodie et al 2009

Despite this evidence, the authors also conclude that additional AEDs can be recommended to patients with epilepsy who fail on two drugs and who are not candidates for epilepsy surgery. The overall the authors suggest that the natural history of epilepsy is that 30% of the patients will be seizure free without treatment and continuing seizures will occur in 40% of patients (Kwan and Sander 2004).

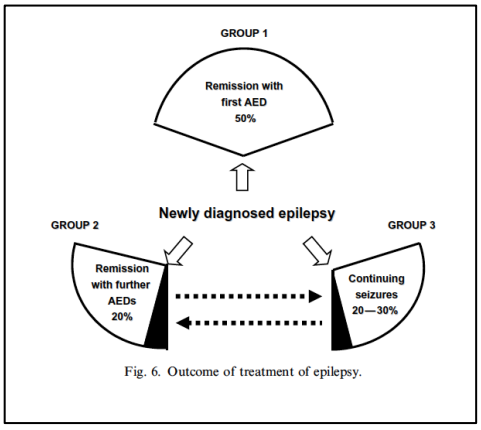


Figure 10 Treatment response to AEDs: Data from Kwan and Brodie: Figure adopted from Schmidt & Elger 2008.

1.4.4 Patients with relapsing and remitting epilepsy

Further work done by Mohanraj and Brodie showed that patients who have responded to AEDs can either be in remission or may relapse (Mohanraj and Brodie 2005). They defined remission is having no further seizures after responding to treatment and relapse was defined as when initial control was lost and patients became treatment unresponsive. The study showed that 57% of patients enter remission when commenced on AEDs. Five percent of patients relapse after a period of response and develop refractory epilepsy and 38% of patients never become seizure free. Rates of

remission were no different in pats with symptomatic epilepsy compared to idiopathic epilepsy.

1.4.5 Seizure freedom and drug resistant epilepsy

A brief discussion of seizure freedom and drug resistant epilepsy is important here as they represent opposites of a continuum of treatment response. Also it is important to define these terms are they have significance in how outcomes are analysed in clinical trials.

The goal of epilepsy treatment is to render the patient seizure free. Kwan et al recently defined what constitutes seizure freedom; this is defined as any patient who is seizure free for at least three times the longest pre-intervention inter-seizure interval in the preceding 12 months. Simply stated, this was named the rule of three. This definition although novel is not clinically useful, it is well known that if seizure freedom is to occur, it would occur early but even patients with chronic epilepsy can become seizure free in 28% of cases (Lucaiano & Shovron 2007). Seizure freedom and reduction in seizure frequency have been the primary goals of epilepsy treatment but quality of life in epilepsy has become important in clinical decision-making.

The converse of seizure freedom is where the patient continues to have seizures despite treatment. This is commonly referred to as drug resistant epilepsy. The mechanism of drug resistance is explained by efflux of drugs by transporter proteins that are found more commonly in patients with multidrug resistant epilepsy. Examples of such protein include multi-drug resistance gene-1 P-glycoprotein (MDR1) and multidrug resistance –associated protein 1 (MDRP1) (Sisodiya et al 2002).

Drug resistant epilepsy was difficult to define as this is regarded as a dynamic state rather than a static state (Téllez-Zenteno, et al 2014). Any definition for drug resistance epilepsy would therefore hold at only one specific period of time. Mohanraj et al suggest that if a patient has failed on at least two AEDs, he or she can be labelled with drug resistant epilepsy (Mohanraj & Brodie 2006). In terms of harms outcomes, one could suggest that some randomised trials that recruit patients that have failed two or more AEDs could provide a useful model for studying harms in drug resistant

epilepsy. The current ILAE accepted definition of drug resistant epilepsy is a " the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules -whether used as monotherapy or in combination, to achieve sustained seizure freedom (Kwan et al 2010).

In many randomised controlled trials that report harms outcomes, included patients would have trials more than one AED and have failed. These trials therefore would provide a model for studying drugs resistant epilepsy.

Up to 30% of patients with drug resistant epilepsy may take a combination of drugs. This will invariably result in drug-drug interactions, particularly with the older AEDs. Classical interactions include the interaction between valproate and lamotrigine where concentration of lamotrigine may increase to toxic levels and cause Stevens Johnson Syndrome (SJS). Another classic interaction is carbamazepine and valproate where adequate levels of valproate are difficult to reach as carbamazepine with lower valproate levels (Schmidt 2009).

The newer AEDs however have less interactions and therefore are less likely to have pharmacokinetic interactions, but this dose not necessarily mean that their harms profile is better than older drugs. It is not clear if the newer AED are able to convert drug resistant to drug responsive epilepsy. Currently however this is no recommendation on which drugs to use in drug resistant epilepsy. However, as we will discuss in chapter seven, several new drugs like lacosamide demonstrated that some patients with drug resistant epilepsy do become seizure free (Weston et al 2015). Similar response in drug resistant epilepsy was noted in trials of perampanel (Faulkner & Burke 2013)

1.4.6 Treatment options in refractory epilepsy

The goal of epilepsy treatment is to render the patient seizure free. There is no single treatment for epilepsy, but there are numerous options depending on the epilepsy syndrome or the stage of the disease.

1.4.7 Surgical options in epilepsy

In general surgery is considered in individuals who have not responded to medical therapy or have had several intolerable harms from antiepileptic drugs or a combination of both reasons. The seizures should be of the type that is amenable to surgical therapy and other electrographic; radiologic and psychological background should support the feasibility of surgical therapy. A decision to proceed with surgery is a multi-disciplinary effort (Spencer & Huh 2008).

Options in surgical therapies include resection therapies where part of the brain or hemisphere is removed. Other options would also include measures to prevent the spread of seizures like corpus callosotomy or subpial resections. If these measures fail then palliative measures such as vagus nerve stimulation is warranted (Ramey et al 2013).

1.5 Alternate Mono-therapy or Add-on therapy?

We know from Brodie's research that with every additional AED used in patients with epilepsy the probability of seizure freedom diminishes with each additional AED (Brodie et al 2009). Their data consisted of two groups of patients; first was a group of patients treated with monotherapy and another groups with polytherapy. The data suggested no significant difference between the two groups with regard to seizure freedom rates. This hypothesis needed to be explored in a randomised controlled trial.

A pragmatic randomised trial carried out by Beghi et al compared adjunctive therapy versus alternative therapy with respect to seizure freedom and tolerability outcomes (Beghi et al 2003). The first figure below shows no statistically significant difference between the two groups with respect to retention (fig 11 page 19). The cumulative probability at 3 months of continuing the drug was 77% for alternative monotherapy and 87% for adjunctive therapy. At 12 months, this was 55% for alternative monotherapy and 65% for adjunctive therapy.

With regard to seizure freedom, this is shown in the figure 12 page 19. The results show no difference between the two groups with respect to seizure freedom. A total of

158 adverse events were noted in the monotherapy group and 111 in the adjunctive therapy group.

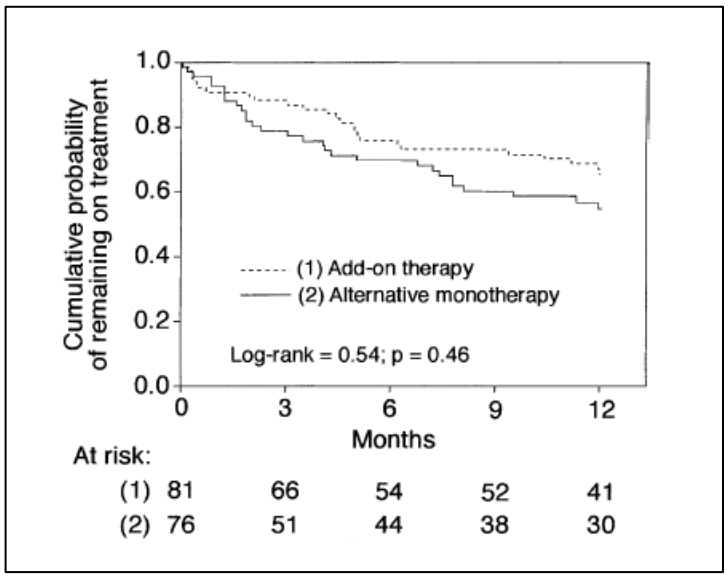


Figure 11 Cumulative probability of remaining on allocated treatment in add-on therapy group versus alternative monotherapy group Adopted from Beghi et al 2003.

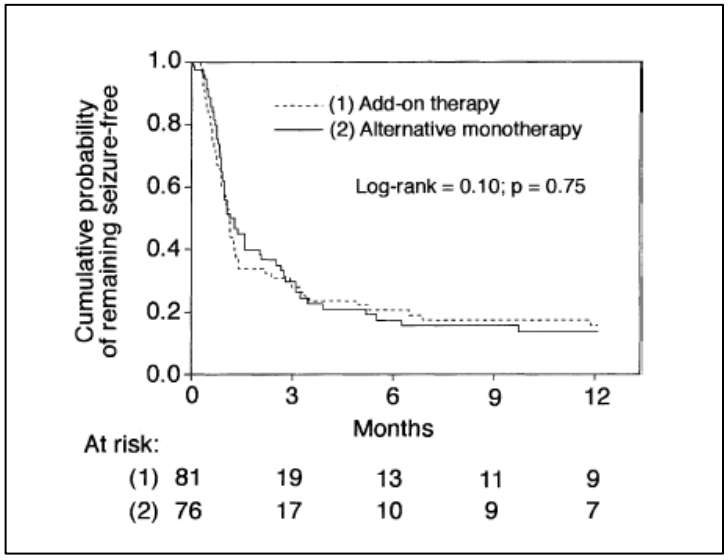


Figure 12 Cumulative probability of remaining seizure-free after achieving target dose in two groups Adopted from Beghi et al 2003.

The mainstay of epilepsy treatment is medical using antiepileptic drugs. Methods for more intractable epilepsy involve either surgical interventions or neuromodulatory treatments. Antiepileptic drugs are significant as they represent about 13% of outpatients' prescriptions in the USA, which is comparable to antibiotics (Raofi & Schappert 2006). Other methods when drugs fail include surgical methods or

neuromodulator methods. The remaining sections discuss the medical and surgical treatment of epilepsy.

1.6 Antiepileptic drugs

There has been a rapid increase in the number of antiepileptic drugs for the treatment of epilepsy in the recent two decades (figure 13). Increasing research by commercial and non-commercial organisations has largely fuelled this growth. The figure below shows that the number of drugs produced has increased exponentially with most of the newer drugs developed in the last decade. Most of the drugs shown here have been modelled on a mouse model of epilepsy and developed under the Anticonvulsant Drug Development Programme in the USA.

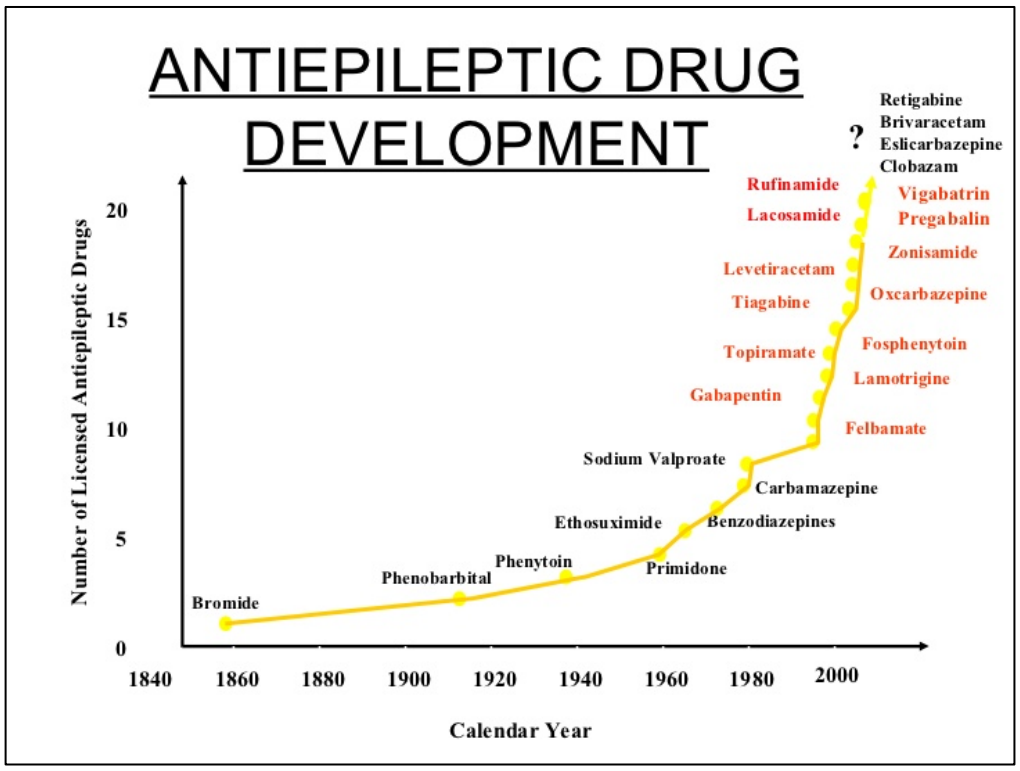


Figure 13 Chronology of antiepileptic drug introduction over the past 150 years. Adapted from Brodie, M. 2010.

1.6.1 Early Antiepileptic drugs

Medications to control seizures were a novel concept in the nineteenth century. The first drug to be used for the treatment of epilepsy was discovered by Charles Locock. He used potassium bromide to treat women with "hysterical epilepsy connected to the menstrual period" and he found that it significantly improved their seizures as well. Thomas Clouston then showed a dose response relationship with potassium bromide in patients with epilepsy in 1868 (Pearce 2002) and since then it has been marketed as a new drug.

Other drugs that were the early AEDs include phenytoin, phenobarbitone, sodium valproate and carbamazepine. Alfred Hauptmann discovered phenobarbitone serendipitously in 1912 by using it as a hypnotic agent in his patients. He observed that patients had significant reductions in daytime seizures and slept better at night too (Hauptmann 1912). Carbamazepine was developed as an antipsychotic drug in 1953 but it was studied in epilepsy in 1963 and gained a licence for use in 1965.
Tracy Putman discovered phenytoin serendipitously in 1934 where he tried to find an alternative to phenobarbitone (Brodie 2010). Phenytoin came into routine clinical use in 1938. Pierre Eymard discovered valproate serendipitously in 1963. The drug was used in Europe as an anti-seizure drug and a modified version of it was used in the USA a decade later.

Levetiracetam was developed as a candidate molecule but it did not show efficacy in many standard models of epilepsy in rodents. However, it did provide protection in two models of epilepsy kindling this was therefore it is only property of levetiracetam (Klitgaard et al 1998).

With the developed of the new AEDs, epileptologists have informally called the older AEDs as the Standard AEDs and the new drugs as the New AEDs (table 5 page 22).

Standard AEDs	Newer AEDs
Bromides	Eslicarbazepine
Oxazolidinediones	Ezogabine
Phenobarbital	Felbamate
Phenytoin	Gabapentin
Primidone	Lacosamide
Ethosuximide	Lamotrigine
Benzodiazepines	Levetiracetam
Carbamazepine	Oxcarbazepine
Valproate	Pregabalin
	Preampanel
	Rufinamide
	Tiagabine
	Topiramate
	Vigabatrin
	Zonisamide

Table 5 List of New and Old Antiepileptic drugs: Adopted from Engel 2013.

1.6.2 How Antiepileptic drugs work

There are three major classes of AED mechanisms that are recognised (Sills & Brodie 2001). These include the modulation of voltage gated ion channels; gamma-aminobutyric acid medicated inhibition and attenuation of glutamate mediated excitatory neurotransmission. Current targets include the voltage gated sodium channels, which are also implicated in epilepsies like severe myoclonic epilepsy of infancy, primary pain syndrome like erythermalgia and some dystonias. Sodium channels are predominantly responsible for action potential generation. Advances in molecular biology have shown a wide number of these channels and how AEDs can interact with them. Some of the newer AEDs interact with sodium channels in a novel way but inactivation of slow channels. Other targets for AEDs include voltage gated potassium channels, calcium channels by modulating their effects on the action potential. The table below outlines the mechanism of the common AEDs used in the past and in current clinical practice (table 6 page 23).

AED	Main Mechanism(s) of Action	Year of Approval (USA)
Old AEDs		
Bromides	Unknown probably stabilises neuronal membranes	1857
Phenobarbital	Enhances GABA inhibition	1920-1940
Phenytoin	Inhibition of sodium channels therefore limiting repetitive firing	1938
Ethosuximide	Reduction of T type calcium channel thresholds in the thalamus, therefore inhibitory effect	1960
Carbamazepine	Inhibition of sodium channels and therefore reducing firing	1974
Valproate	The precise mechanism unknown; multiple GABA related actions and NMDA receptor antagonist.	1978
Newer AEDs		
Vigabatrin	Irreversible inhibition of GABA receptors and stimulates GABA release	2009
Felbamate	Binds to NMDA glutamate receptors and therefore blocking sodium and calcium and conduction	1993
Gabapentin	Precise mechanism is unknown but may bind to voltage gated calcium channels	1993
Lamotrigine	Blocks sodium channels and inhibits voltage gated calcium channels	1994
Tiagabine	Enhances GABA mediated inhibition by blocking GABA reuptake	1997
Topiramate	Multiple mechanisms: it blocks AMPA glutamate receptors, blocks of voltage activated sodium channels; enhances GABA mediated chloride flux and enhances potassium conduction.	1997
Levetiracetam	The precise mechanism unknown but it binds to SV2A presynaptic protein on synaptic vesicles.	1999
Oxcarbazepine	Blocks of voltage gated sodium potassium and calcium conduction.	2000
Zonisamide	Blocks T type calcium channels, inhibit release of glutamate.	2000
Rufinamide	Exact mechanism unknown but prolongs the inactivation of voltage-dependent sodium channels	2005
Lacosamide	Selectively alters the slow inactivation of voltage gated sodium channels.	2008
Perampanel	AMPA receptor antagonist but not NMDA receptors	2012

Table 6 Antiepileptic drugs mechanisms of action. Adopted from French & Gazzola 2011.

1.6.3 Specific AEDs

To discuss all the AEDs used in clinical practice is not the scope of this thesis. However lacosamide will be discussed as it is the focus of chapter six .

1.6.3.1 Lacosamide-mechanism of action

The mechanism of action of lacosamide remains unknown, however there are a number of potential theories. Lacosamide was developed from a bank of compounds

designed to interact with voltage gated sodium channels (Stoehr 2004). Lacosamide is related to a d-serine amino acid, its chemical name is (R)-2-acetamido-N-benzyl-methoxypropionamide. It has been shown to modulate voltage gates gated sodium channels by a dual mechanism. Lacosamide increases the inactivation of slow sodium channels with no effect on fast inactivation. Fast inactivation that lasts a few milliseconds is how other sodium channel blockers work but lacosamide works by increasing slow inactivation, which lasts up to a second. This dual mechanism effects neuronal hyper-excitability and therefore on the propagation of seizures (De-Biase et a 2014).

Finally, lacosamide may also interact with N-type calcium channels and influencing calcium currents in epilepsy. However recent experiments by Khanna and Wang did not prove any change in calcium currents when lacosamide was studies using patch clamp methods (Wang & Khanna 2011).

1.6.3.2 Lacosamide- pharmacokinetics

Lacosamide is rapidly absorbed after oral administration. Absorption is not affected by food intake (Contin et al 2013). Maximal plasma levels of lacosamide are reached between 1 and 4 hours after oral intake. Dose kinetics is linear and 40% of the drug is excreted unchanged in the urine. Thirty percent of lacosamide is metabolized to an inactive metabolite. The plasma half-life of lacosamide is 13 hours allowing for twice daily dosing. Multiple dosing did not change the basic pharmacokinetic properties (Cawello et al).

Given lacosamide have different interactions with sodium channels when compared to other AEDs; it therefore does not interfere with the action of other AEDs at other sites of sodium channel binding. There are no drug to drug interactions reported however longer term studies have indicated that drug inducing AEDs like phenytoin, carbamazepine and phenobarbital can decrease the dose of lacosamide by 25%. This result was borne out in a recent study (Contin et al 2013).

1.6.4 Other AEDs in development

The development of new models in epilepsy has produced a number of molecules that have recently undergone phase three trials. Development of these newer AEDs has paralleled with new in vitro and in vivo models for epilepsy. Some new AEDs are made from modifying existing AEDs and these are developed as new molecules or serendipitously. Examples of AEDs with new chemical structures include; ganaxolone, rufinamide and YKP3089. AEDs that have undergone modification of existing AEDs include bivaracetam, which is a modified form of levetiracetam. Other modified novel AEDs include ICA 27243, JZP-4, licarbazepine and MTMCD.

1.7 Conclusion

Epilepsy is a chronic condition that affects both the physical and social aspects of a patient's life. Patients with epilepsy are faced with long term treatments, which may be toxic or associated with cognitive impairment. Epilepsy is a common disease and accounts for a large number of hospital and clinic admissions. All age groups are affected by epilepsy, but the incidence of epilepsy peaks in young children and the elderly.

This chapter discussed the current developments in epilepsy. Some of these advances have been profound, as they have changed clinical practice. These changes have revised some the fundamentals of epileptology like the definition of epilepsy and when to initiate treatment. Alongside this, there has been an explosion of new antiepileptic drugs and a greater understanding of the molecular mechanisms of epilepsy (Doeser et al 2015). Alongside this new research into when to treat epilepsy and seizures have led to novel research on when to treat seizures and epilepsy.

Having a first seizure can be frightening to many patients. Patients would often ask about the odds of having a subsequent seizure and if they indeed have epilepsy. Certainly, one can make a diagnosis of epilepsy if two or more seizures have occurred. Whereas if only one seizure has occurred then recent data from large studies like the MESS study have informed us that the risk of immediate versus deferred treatment after a first seizure overall is not different. This is clinically important as it highlights that deferring treatments will not worsen the prospects of becoming seizure free. This is especially important if the patient is at a low to medium risk in having further seizures. Other studies have been able to stratify this risk using findings from neurologic exam, EEG and imaging criteria. Such risk factors include a history of trauma, remote history of febrile seizures and generalised spike and wave activity in the EEG.

Recent changes to the definition of seizure freedom have occurred also in light of studies by Kwan and Brodie et al (2009). Their data examined the proportion of patients rendered free of seizure after the first and second antiepileptic drug. Despite many attempts to formulate a definition of seizure freedom, this recent definition is

interesting but not clinically useful. The likelihood of becoming seizure free is good with 50% of patients being seizure free after first monotherapy drug and 20% after the second drug is added. This decreases to 18% when the third a subsequent drug is added and there may be patients that may never be seizure free no matter what drug is given to them. Data like this is also useful in epilepsy clinics when patients are unsure about whether they want to continue treatment or when they want to initiate treatment. Logically the next question patients ask is which drug out of a large number of drugs is the best choice for their particular type of epilepsy. Information of the best drugs for epilepsy has been informed by clinical trials and by clinical guidelines.

Much of the evidence for this is from observation and traditional practice. Furthermore, the population of patients that are seen in the first seizure clinic are not the same as the patients that are recruited into clinical trials. The sheer number of new AEDs makes deciding the best treatment for a given patients more difficult. Randomised controlled trials so far have comparative information on whether a drug is preferable to placebo. They however lack data on when these drugs should be started and there is little data on which drugs are better than others. Other potential sources of evidence are clinical practice guidelines (CPG). A recent review of guidelines of the initial management of epilepsy by Payakachat et al showed that many of the guidelines included evidence for trials published between 1980 and 2006 but the key organisations like NICE, AAN and SIGN mentioned older AEDs and the AAN advised using AEDs which not under licenced for their indications (Payakachat et al 2006).

This chapter introduced epilepsy, seizures and the numerous drugs that have been developed so far. Nonetheless, one quintessential aspect of the doctor-patient consultation is the issue of harms. It is very common for patients to ask about side effects of AEDs especially if the duration of treatment is lifelong. Data for harms of antiepileptic drugs is lacking and this needs to be addressed. This will be the focus of chapter four. The next two chapters discuss the concept of clinical trials and the rationale behind clinical trials.

Chapter 2

Evaluating harms in clinical studies of antiepileptic drugs

2.1 Introduction

The previous chapter discussed the diagnosis of epilepsy and its management and how research has changed the management of a patient with a first seizure. Patients are also faced with various treatment options Differing mechanisms of actions of antiepileptic drugs have led to ideas such as rational polytherapy where certain combinations of medications of drugs may produce better outcomes in patients with epilepsy. Clinical trials in epilepsy have provided answers to many of these questions. This chapter considers the various sources of evidence that clinicians have used to make treatment options, the concept of evidence-based medicine and the pivotal trials in epilepsy.

2.2 Hierarchy of evidence

Any observation made could be counted as evidence. Evidence can vary from simple observations to more complex constructs like randomised controlled trials (RCTs). The key step in evidence-based medicine is to grade the evidence into meaningful hierarchies. This then allows for recommendations based on the strength of evidence.

In 1992, the journal JAMA discussed in a paper of a paradigm shift in medicine where decision-making is supported on evidence rather than clinical experience. The Evidence Based Medicine group who are authors of this article called the new paradigm as evidence base medicine (Guyatt et al 1999).

The centre of evidence-based medicine in Oxford describes a hierarchy of evidence (Oxford Centre for Evidence Based Medicine 2009). The highest level of evidence is a well-conducted systematic review. Individual patient data systematic reviews are the highest level of evidence (Stewart & Parmar 1993). In relation to AEDs Chadwick and Marson discussed that the hierarchy of evidence is similar but not the same as described above. The relative hierarchy of the expert opinion is higher than the case report (Chadwick & Marson 2007).

The lowest form of evidence is unsystematic observations; this is where observations of patient's response to a given treatment are utilised to guide treatments in other patients. Some clinicians call this form of evidence - an "expert opinion". The next

level in the hierarchy is where a number of observations are collected into a case report or even a series of observations found in different patients to form a case series. Case reports are by themselves useful for rare and uncommon diseases but they are prone to bias. A collection of case reports can be further elaborated into a review article but this does not decrease bias as the selection of cases by authors may lead to alternate conclusions. Case controlled study designs are the next level of evidence. They are useful when the conditions are rare and the aims are to identify the risk factors for the development of disease. These studies are retrospective in design where comparison between cases and controls helps elucidate risk factors.

2.3 4 Clinical trials

The word clinical comes from the Greek *kline* which means bedside. Clinical knowledge was traditionally based on the collective experience of doctors and from observations and based on pathophysiological data. The theoretic background to this is based on established biology, pathology and pharmacology. Mathematical and statistical sciences are based on objective data supported by theorems and mathematical models. When the two disciplines of clinical medicine and mathematical statistics were combined, one can argue that this formed the basis of clinical trials.

Societal expectations and pressures have also meant that doctors can no longer use their experience to make treatment decisions. Increasingly doctors and drug companies alike need to persuade patients and licencing bodies that the treatments they offer are safe and effective for patients. Austin Bradford- conducted the first clinical trial in 1948 (Hill 1961) (Yoshioka 1998). He compared streptomycin for the treatment of pulmonary tuberculosis. Over the past century, there has been an explosion in the number of trials.

2.3.1 Design of a Clinical Trial

There are several ways in which a clinical trial can be conceived. Conventional trials have an active intervention and a comparator group (fig 14 page 31). They can be conceptualised as having a baseline phase, a titration phase and a maintenance phase. Patients can be randomised into one or more arms where one is an active intervention

and the other is a comparator, which may or may not be placebo. Trials can have several active intervention arms and one comparator or can have several arms allowing for multiple pairwise comparisons.

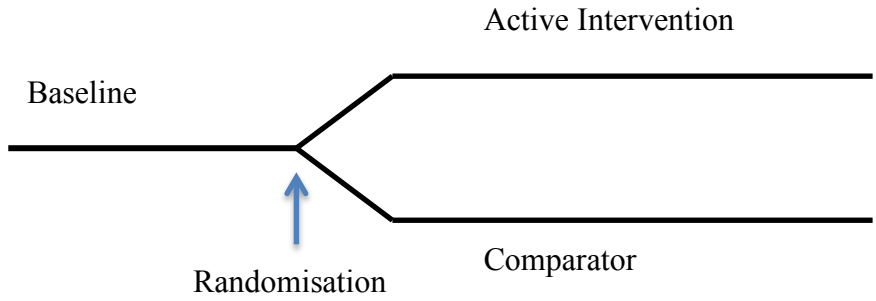


Figure 14 Conceptual framework of a clinical trial: Adapted from Systematic reviews of randomised controlled trials of antiepileptic drugs, (Marson 2000).

A key concept of a clinical trial is that patients differ only with respect to treatment allocated and not any other characteristics. If the treatment groups differ in some way other than the comparison of treatment, then the comparison is referred to as biased. Randomised clinical trials, patients and trial administrators are kept unaware of the nature and type of intervention. The key goal of clinical trials is to demonstrate the efficacy of a drug or intervention. This is achieved in comparison with placebo to demonstrate superiority or another active intervention to demonstrate either superiority or equivalence. Consequently trial methodologies have evolved to answer specific questions.

How treatments are allocated to patients is quintessential to the validity of RCTs. The generation of unpredictable allocation sequence is an essential element of randomisation in a RCT. Randomisation eliminates selection bias; randomisation also permits the use of probability theory to explain any differences in outcomes that occur (Schultz et al 1995). This is achieved by adequate generation of allocation. The allocation should be concealed from patients and assessors. Allocation concealment also reduces bias in ascertainment where treatments don't influence the assessment of patients (Schultz & Grimes 2002).

Randomisation can be simple randomisation, blocked randomisation or stratified randomisation. Simple randomisation is with a single ratio i.e. a 1:1 ratio of equal

number of patients assigned to interventions. Blocked randomisation is where a block of patients with one variable, are entered and this eliminates nuisance factors as a source of variability. Stratified randomisation is where a set of characteristics of patients is randomised in such a way to allow subgroup analysis to occur. Strata like age and sex can be utilised.

Blinding of trials is important to reduce bias. Blinding can be single blinded where the allocation is hidden from either the patients or the assessor or double blinded with both assessor and patients are blinded to the allocated treatment (Sibbald & Roland 1998).

Allocation bias is where the treatment is given to patient in a random manner and there is no way of predicting which treatment will be allocated to a given patient. The types of biases that are reduced by blinding include allocation bias and ascertainment bias.

2.3.2 Types of trials

There are various ways in which to classify clinical trials. For the purpose of this thesis, this classification has been simplified (table 7 page 33). Parallel group trials are the commonest trials where there are at least two parallel arms. These could include a placebo or another active comparator. Parallel trials can be either mono-therapy studies where the intervention arm is a single drug or add-on therapy where the intervention is added to a pre-existing intervention.

Selai & Trimble discussed the notion that antiepileptic drugs can be prescribed as an add-on to an existing AED in 1998. In their study, they interviewed patients with epilepsy and observed that 17% of patients with add-on therapy had benefited from the newer AED (Selai & Trimble 1998). Add-on trials are common because most AEDs would need to obtain an add-on licence and then be approved for monotherapy. The reasons for this are that it would be unethical to study a new AED as monotherapy before it is awarded an add-on licence.

Common trial type	Description
Placebo controlled add on studies	A study in which the drug is compared with the effect of a placebo. Experimental drug is taken with other regular medications affecting the intended outcome. Outcome are predefined and adverse events are usually short term adverse events
Placebo controlled mono therapy studies	A study in which the drug is compared with the effect of placebo. Patients are not on any other drugs that may mimic the effect of the intervention
Actively controlled studies	No placebo in the comparator group but two or more active interventions
Pragmatic studies	Here the trial explores differences between treatments, where the allocated treatments are used routinely used in clinical practice
Observational Studies	There is no comparator arm and patients are allocated the active intervention or interventions. There are useful for detecting long term outcomes or adverse events

Table 7 Common types of Clinical Trials.

2.3.3 Other Clinical Trials in Epilepsy

This section briefly discusses other trial types used in epilepsy. A brief note here is necessary as some of these trials are mentioned in chapter three. Examples of such trials include: Pre-surgical trial where patients intending to have surgery are withdrawn from AED and may be given another intervention or placebo for a short period of time. Conversion to monotherapy trial is where the drug of interest is maintained and any add-on drugs taken by the patient is one withdrawn. This is one way of transforming an add-on trial to a monotherapy trial. An actively controlled trial is where the comparator is not placebo but a different AED. The outcome of such a trial is to demonstrate equivalence.

2.3.4 Special Clinical trials: Pragmatic, trials

The term pragmatic trial was coined by Schwartz and Lellouch (1967). These trials assess interventions in that natural clinical setting compared to parallel trials where the conditions are strictly controlled. These trials are designed reflect the real world and as such are highly sought after by policy makers and patients. Usually the interventions do not include a placebo group and intervention in pragmatic trials could be a drug

intervention or any other intervention. Pragmatic trials are however open to bias, as they may not blinded (Zwarenstein et al 2008). The table below illustrates the differences between pragmatic and exploratory trials.

Item	Exploratory trial	Pragmatic trial
Question	Efficacy- can the intervention work?	Effectiveness- does the intervention work when used in normal practice?
Setting	Highly selected. Poorly Adherent participants and those with conditions that might dilute the effect are excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence monitored	Allows flexibly as would be normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to practitioners, funders, communities, and healthcare practitioners
Relevance to practice	Indirect relevance	Direct relevance and is the key reason for trial conduct.

Table 8 Key differences between trials with explanatory and pragmatic stidies, adapted from Zwarenstein et al 2008.

2.4 Clinical Drug Development

Clinical trials are often classified into four main phases (table 9 page 35). These take into account development of the drug of interest and communicate the extent of drug development. These have been called Phase I, II, III and IV. Regulatory trials are phase IIa, IIb and phase III studies. Phase 2a studies evaluate the efficacy and safety of the intervention with the aim to assess dose range and response. Phase 2b is a definite dose finding studies. Regulatory trials are also called exploratory trials, which contrasts them with pragmatic trials. Phase IV is a post marketing study after the licence is approved and the sponsors are interested in long-term outcomes or adverse events.

Old terminology	Descriptive terminology
None	Translational studies
Phase I	Treatment Mechanism TM studies
Phase I	Dose Finding DF studies
Phase I	Dose Ranging studies
Phase II	Safety and activity studies SA
Phase IIa	Safety and activity studies SA
Phase IIb	Comparative Studies CTE
Phase III	Comparative Studies CTE
Phase IV	Expanded safety ES
Large Simple	Large Scale studies

Table 9 Classification of clinical trials by phases.

The Medicines Healthcare Products Regulatory Agency (MHRA) is the local UK based regulatory authority that issues licences to market drugs for clinical use. The Food and Drug Administration (FDA) is the authority based in the USA and the European Medicine's Agency (EMEA) is located in the European Union. An EMEA approved drug would also automatically meet MHRA approval. A licence would be issued if the drug sponsors provide two phase III trials that have proved efficacy and safety.

When antiepileptic drugs are considered, the EMEA has produced a draft guideline in the development of drugs as add on therapy and for the development of drugs to specific epilepsy syndromes as advised by the ILAE. The EMEA would allow the registration for an add-on indication if two or more trials show proven efficacy and safety. A monotherapy indication is granted if the drug has been given a licence as an add-on indication in newly or recently diagnosed patients. If a drug has a trial in another indication, then the regulatory authorities need only one successful trial to show further efficacy (French 2012). Monotherapy trials are relatively uncommon, but if they were more common, then they would provide good evidence of efficacy against placebo. Some of these trials have been not been sponsored by drug companies and compare older AEDs like carbamazepine or valproate where the comparator is not placebo but a low functioning dose of the active drug. Monotherapy trials of newer AEDs are uncommon as it would be unethical to subject some patients to placebo.

Regulatory authorities store unpublished trial data provided by drug sponsors Recent unpublished data for clinical trials can be accessed from the websites of the EMEA and the FDA, but these are hampered by the complex nature of their webpages. Further they do not index trial data making it difficult to match data to published reports available to the researcher (Schroll et al 2015) (Howie et al 2013).

The Clinical Trials Directive number 536/2014 of the European Union comes to force in 2016. This directive will let the EMA to form a single portal of entry for documents to be submitted. The directive also requires that there be transparency of outcome measures however they fall short with harms outcomes and requires that not al harms outcomes need be reported for regulatory approval (European Commission 2014).

2.5 Outcome measures in clinical trials of epilepsy

There are several outcome measures used in trials of epilepsy. A report by the commission on outcome measurement in epilepsy in 1998 outlined these outcome measures (Baker et al 1997). The key outcomes are described here. Outcomes in epilepsy can be broadly classified as efficacy outcomes, harms outcomes and quality of life outcomes. When considering efficacy and harms outcomes one must distinguish between outcomes that are needed for regulatory trials and outcomes that are reported in non-regulatory trials.

2.5.1 Efficacy Outcomes

Types of efficacy outcomes needed in regulatory studies could vary if the trial is an add-on study or a monotherapy study. In add-on studies, the duration during which seizures are assessed need to be predefined. The commonest primary outcome is a percent reduction of seizure frequency and the proportion of patients with seizures decreased by a pre-defined amount over a defined period. Typically, this is a 50% reduction in seizure frequency over 12 weeks. Other secondary measures outlined by the EMA could include:

1. > 25% worsening, no change, > 25% reduction, > 75% reduction
2. Seizure severity and duration of seizures

3. Validated scaling measures
4. EEG patterns
5. Seizure counts by the patient or caregiver
6. Seizure freedom

Critics of these standard measures state that outcomes such as seizure frequency will underestimate the true treatment effect; they argue that if patients have two seizures in the same day, it may be counted as one seizure if recorded in diaries. A better estimate is the 50% reduction in seizure frequency as this can allow for comparisons across and between trials (Baker et al 1997).

Other time to event outcomes used in trials include time to 12-month seizure remission and time to withdrawal due to harms.

2.6.2 Tolerability Outcomes

Usually tolerability outcomes are secondary measures. The most common is the proportion of patients that withdrew from the study due to any reason including adverse events. Trials would commonly report the number withdrew due to a violation of protocol and would report then number that withdrew due to harms separately. Some trial would further elaborate on the specific adverse event or events, which lead to withdrawal of the patient.

2.6.3 Harms Outcomes and Adverse Events

Harms data of adverse events are usually reported in clinical trials with varying levels of detail and completeness. Trials differ in the number of adverse events reported and in the degree of detail they provide regarding each adverse event.

Commonly the measure of tolerability of treatment is reflected in the proportion of patients withdrawn due to adverse events. This is usually expressed as a total number of patients or as a percentage of patients withdrawing due to adverse events. Trials quote specific adverse events that have occurred during the treatment period. Commonly these would include dose related adverse events like nausea or dizziness.

Rare and idiosyncratic adverse events are sometimes reported; examples of these include Toxic Epidermal Necrolysis (TEN) or Steven's Johnson Syndrome (SJS).

The level of detail provided by individual trials differs too. Some trials will only provide summary measures of discrete adverse events as a percentage figure. Some trials are more specific and provide the number of adverse events, but this does not provide details if they occurred in the same patient or not. Uncommonly trials would mention if patients reported two or more adverse events with elaborate details.

Majority of adverse events reported in RCTs are dose related and therefore transient. One study by Majkowski in 2005, examined the incidence of harms from unpublished data obtained from several topiramate studies. Their findings illustrate that most harms occur during the titration period as opposed to the baseline phase, but the types of adverse events do not differ between trial phases. They conclude that dose related harms are common and could be reduced in RCTs with slower titration. (Majkowski 2005). This study shall be discussed in detail later as it provides a useful model of analysing adverse events.

2.5.4 Quality of Life measures

It is noteworthy that regulatory trials are not required by the EMA to provide quality of life data. There are a large number of quality of life measures that can be employed in RCTs. These scales are designed to assess the patient in the inter-ictal state where they may suffer from the psychosocial consequences of epilepsy and side effects of treatment. A summary of the common measures is set out in the table below (table 10 page 39).

Scale	Reference
Quality of life in epilepsy QOLIE-31, 10, AD-48	Cramer et al 1998, 1996, 1999
Liverpool HRQOL Battery	Baker et al 1994
Impact of epilepsy scale	Jacoby et al 1993
NEWQOL	Abetz et al 2000
Epilepsy surgery inventory ESI-55	Vickrey et al 1992
Impact of Childhood illness	Hoare& Russell 1995
Children's QOL in Epilepsy Survey	Wildrick et al 1996
Epilepsy foundation of America (EFA) Concerns index	Gilliam et al 1999
QOL in Paediatric Epilepsy Scale	Arunkumar et al 2000

Table 10 Epilepsy specific health related quality of life outcomes: adapted from Privitera & Ficker 2004.

2.5.5 Liverpool Adverse Events Profile

The Liverpool Adverse Events Profile (LAEP) is a self-assessment questionnaire that is commonly used in clinical trials for the assessment of adverse events. The LAEP consists of 19 items using a four point Likert scale. It is valuable as it only takes ten minutes to complete. It proves useful as it can extract specific adverse events from patients. A study by Gilliam in 2004 showed that if patients were asked to complete the LAEP in clinic; they are three times more likely to report harms to their doctor in consultation and are three times more likely to have their medication reduced as a consequence (Gilliam et al 2004b). The study also showed that the use of the LAEP resulted in a significant reduction in adverse events in the four months following the completion of the initial use of the LAEP. Interestingly in this study, secondary outcomes showed that 31% of patients in routine clinical practice have adverse events. A major drawback of the LAEP is it may not capture all adverse events.

2.6 Limitations of RCTs informing on harms of AEDs

Randomised controlled trials and observational studies are the most common source of evidence for efficacy and harms outcomes. This section discusses the merits of both RCTs and observational studies.

Randomised controlled trials are better at providing more accurate estimates or information about treatment effects. They are less prone to bias due to the design

features of RCTs and therefore provide better estimates. One of the disadvantages of RCTs is that they will not detect long-term harms, as trials are short duration. RCTs are better at efficacy outcomes and short-term harms but not for long terms harms outcomes. These other outcomes may be better studied in observational studies.

Commonly observational studies are follow-up studies at the end of a randomised controlled trial or they can be independent studies. They are usually unblinded and they lack allocation concealment and random allocation in their design. As a consequence of this, they are open to bias and owing to the heterogeneous nature of these trials, it is not always possible to synthesise them in to a higher form of evidence like a systemic review.

Observational studies have been known to overestimate treatment effects. This has hitherto been the main argument of not including these studies in systematic reviews. Nonetheless, a study by Ioannidis (2001) has found very good correlation between randomised and non-randomised studies; in one study the Pearsosn's correlation between summary odd ratios of randomised and non-randomised trials was 0.75 with a p value of < 0.01 (Ioannidis et al 2001) this suggested that summary measures do not differ much. In contrast to this study, Maguire et al combined summary measures from observational studies of AEDs and found, they varied extensively, treatment estimates were therefore unreliable and therefore cannot be used in systematic reviews (Maguire et al 2008).

Observational studies have benefits over RCTs in that they are longer in duration and do not possess fixed doses and titration schedules. Other arguments that favour observational studies over RCTs are that they as more closely related to clinical practice. RCTs also ignore patient's characteristics and just compare survival curves or the outcomes therefore this allows generalizability of results across trials into systematic reviews. One example of where observational studies has been useful is the description of persistent visual field defects found in patients taking long term vigabatrin. The association of visual field defects was noted in a case reports of patients and then this was confirmed in a large scale observational study (Lawden et al 1999) (Comaish et al 2000) This association of visual fields defect was not found in randomised controlled trials.

Other sources of harms data include large databases like the yellow card reporting system. Such systems are pharmaco-vigilance systems set up either by drug companies or by other organisations to collect and publish alerts of rare and potentially serious adverse events caused by drugs.

The remainder of the chapter discusses important trials in epilepsy and epilepsy and information on which drugs to choose for their patients. The evidence pertaining to best drugs after first and second seizure was discussed earlier. The next section discusses evidence of the best AED for a given group of patients with epilepsy.

2.7 Pragmatic studies in Epilepsy.

Clinical guidelines published by organisations like the AAN or ILAE have been informed by RCTs and some of the older published guidelines were difficult to assimilate as they were informed by placebo-controlled trials. These recruited patients often refractory to treatment and this population was considered somewhat artificial. Pragmatic studies were developed to study an AED or a group of AEDs in a mixed population of patients that simulated routine clinical practice. Unlike RCTs these were longer in duration too and allowed long term AE to be assessed. The largest pragmatic study to date is the SANAD study.

The Veterans studies conducted in the USA were the first studies that looked at the best choices of AEDs would be in patients with epilepsy. A study by Mattson et al compared phenytoin, phenobarbital, primidone and carbamazepine in a randomised manner and found that they differed not in efficacy but in their side effects profiles (Mattson et al 1996). Another study by Heller et al compared valproate, phenobarbital, phenytoin, and carbamazepine in patients with generalised tonic clonic and partial seizure. This study found no difference in time to 12-month seizure freedom but they differed in terms of adverse events (Heller et al 1995). The overall conclusion we can make is that likely drugs do not differ much in their efficacy measure but only adverse events. Head to head comparison of randomised controlled trial also can be misleading. One study comparing carbamazepine and lamotrigine could not be considered as reasonable evidence as the steep escalation phase showed a large number of patients that dropped out of the trial the outcome at the end of this trial showed that

there was no difference between the two drugs (Brodie et al 1995). A recent review using individual patient data was the best source of evidence comparing one drug over another this showed no difference between carbamazepine versus valproate (Marson et al 2002) but the methods used in the meta-analyses was carried over to determine the efficacy of one drug over another trial in a prospective manner. This was the SANAD study.

2.8 The SANAD study

In routine clinical practice drugs such as valproate, topiramate, lamotrigine and possibly levetiracetam are useful in patients with both generalised and focal epilepsy. Other drugs like carbamazepine, phenytoin and ethosuximide can aggravate seizures in idiopathic epilepsy but are useful in focal epilepsy. One large pragmatic study called the Standard And New Antiepileptic Drug study (SANAD).

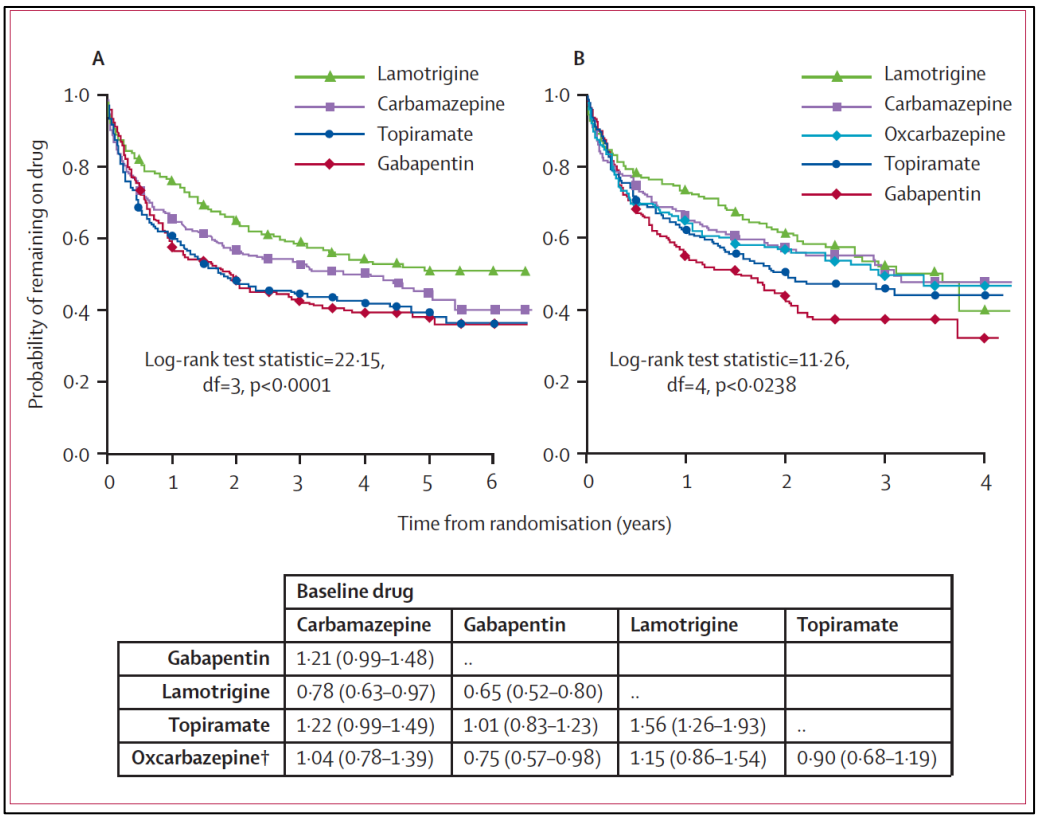
The aim of the SANAD study was to compare one standard drug for focal epilepsy (carbamazepine) in arm A with newer AEDs, and one standard drug for generalised epilepsy (valproate) in arm B with newer AEDs (Marson et al 2007) (Marson et al 2007).

The SANAD study was an unblinded multicentre study where at the time of diagnosis the clinician would need to make a decision whether patient's epilepsy would be better treated with either carbamazepine or valproate. Also, there was no evidence on the best drug for partial epilepsy, as there existed only one individual patient data systematic review of carbamazepine. For generalised epilepsy, the evidence of valproate being superior to other AEDs was from observational studies. Clearly this lack of evidence needed addressing.

The SANAD study was composed of two arms. 1721 patients were recruited into arm A and 716 patients were recruited into arm B. Primary outcomes were the time to treatment failure (due to adverse events or inadequate seizure control or combination of the two) and time to achieve a 12-month remission of seizure. Other outcomes were time from randomisation to first seizure; time to achieve a two-year remission and

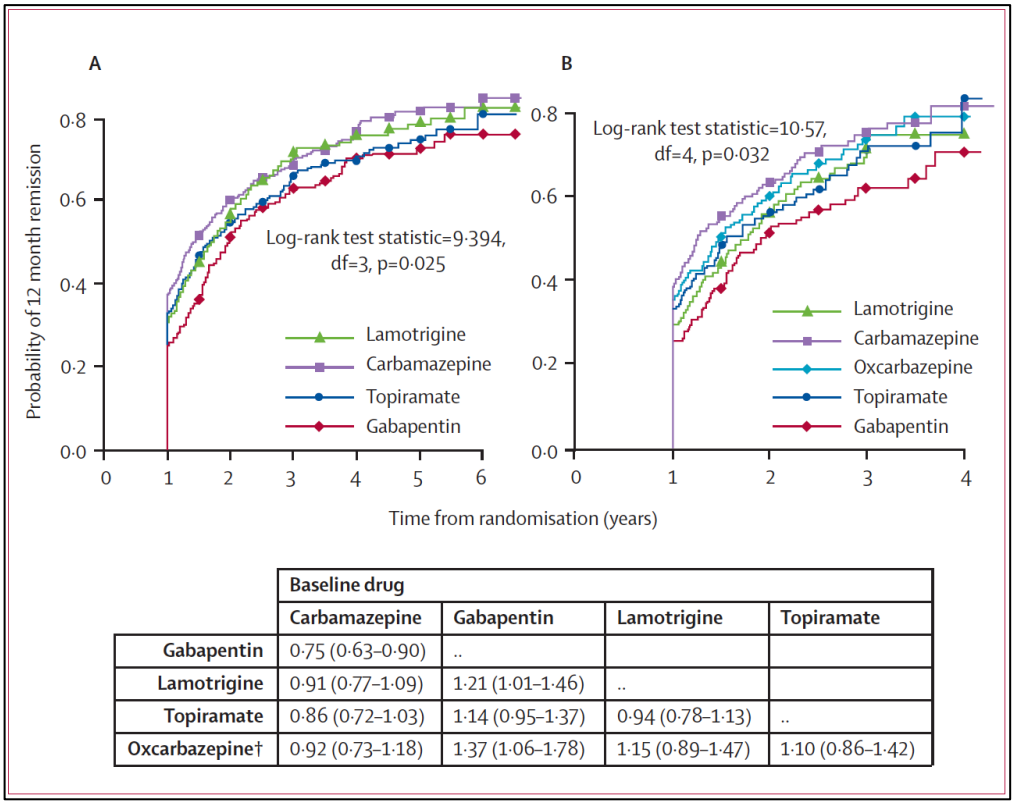
frequency of clinically important adverse events. This study was partly funded by commercial sponsors.

For time to treatment failure in SANAD arm A, two plots are displayed due to oxcarbazepine being introduced later in the trial (Marson et al 2007). For time to treatment failure lamotrigine performed better than the other drugs. Pairwise comparisons showed hazard ratios in favour for lamotrigine against carbamazepine, gabapentin and topiramate (see fig 15 page 43). For time to 12-month remission one sees that topiramate and oxcarbazepine are the least favoured and carbamazepine and lamotrigine are most favoured. The lower treatment failure rates for lamotrigine was due to better tolerability therefore the balance of risks would therefore favour lamotrigine over carbamazepine for treatment of partial seizures (see fig 16 page 44).



	Baseline drug			
	Carbamazepine	Gabapentin	Lamotrigine	Topiramate
Gabapentin	1·21 (0·99–1·48)	..		
Lamotrigine	0·78 (0·63–0·97)	0·65 (0·52–0·80)	..	
Topiramate	1·22 (0·99–1·49)	1·01 (0·83–1·23)	1·56 (1·26–1·93)	..
Oxcarbazepine†	1·04 (0·78–1·39)	0·75 (0·57–0·98)	1·15 (0·86–1·54)	0·90 (0·68–1·19)

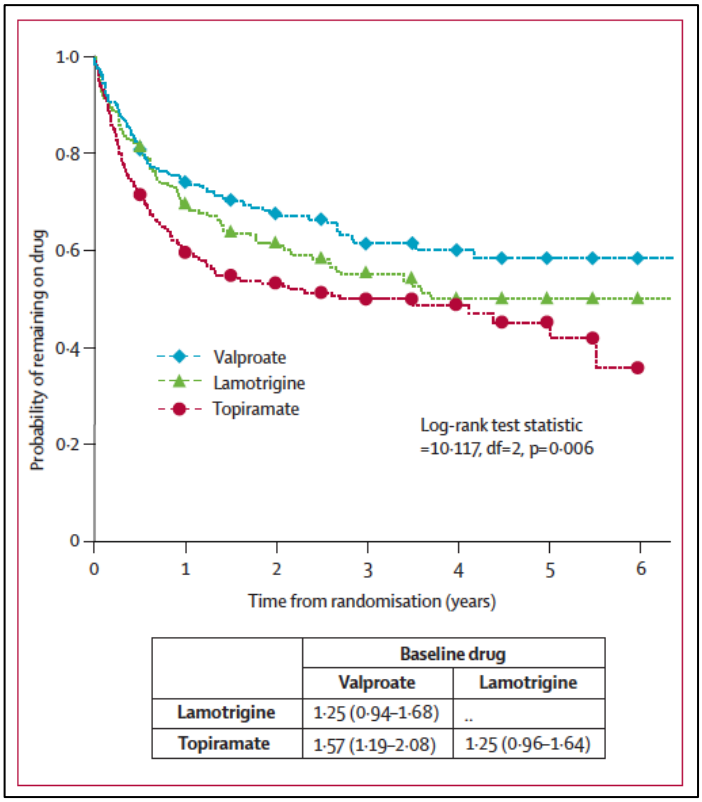
Figure 15 Time to treatment failure in patients enrolled in SANAD arm A. First graph shows whole population and second shows data including oxcarbazepine. Hazard ratios of failure of drug when added to baseline drug (Marson et al 2007)



	Baseline drug			
	Carbamazepine	Gabapentin	Lamotrigine	Topiramate
Gabapentin	0·75 (0·63–0·90)	..		
Lamotrigine	0·91 (0·77–1·09)	1·21 (1·01–1·46)	..	
Topiramate	0·86 (0·72–1·03)	1·14 (0·95–1·37)	0·94 (0·78–1·13)	..
Oxcarbazepine†	0·92 (0·73–1·18)	1·37 (1·06–1·78)	1·15 (0·89–1·47)	1·10 (0·86–1·42)

Figure 16 Time to 12-month remission for whole population and for oxcarbazepine data. Hazard ratio of greater than 1 indicates failure occurs more rapidly on drug compared with baseline (Marson et al 2007)

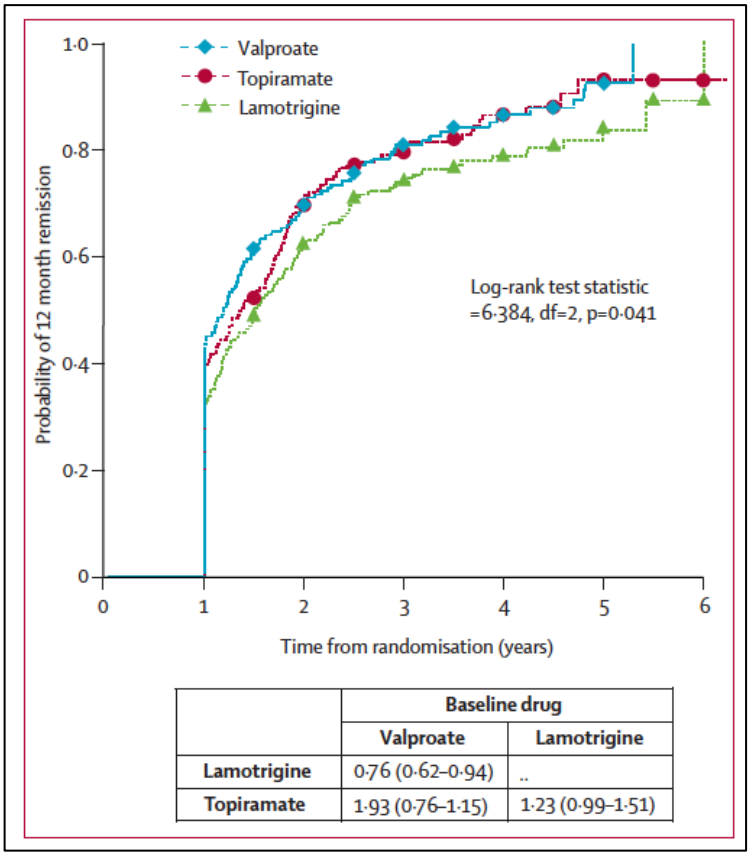
SANAD arm B evaluated valproate, lamotrigine and topiramate in patients with generalised or unclassifiable epilepsies. In arm B, the time to treatment failure for valproate was significantly better than topiramate but there was no difference between lamotrigine and valproate. This was noted in pair wise comparisons and noted when the probability of staying on lamotrigine, valproate and topiramate was plotted against the duration of the trial, see fig 17 page 45.



	Baseline drug	
	Valproate	Lamotrigine
Lamotrigine	1·25 (0·94–1·68)	..
Topiramate	1·57 (1·19–2·08)	1·25 (0·96–1·64)

Figure 17 Time to treatment failure for patients allocated to lamotrigine, topiramate or valproate in patients with idiopathic generalised epilepsy or unclassified epilepsy. Plotted as the probability of staying on treatment (Marson et al 2007)

For time to 12-month remission, about 80% of patients entered into 12-month remission in the first year. The probability was greatest for valproate followed by topiramate and followed by lamotrigine for the duration of the trial (fig 18 page 46).



	Baseline drug	
	Valproate	Lamotrigine
Lamotrigine	0·76 (0·62–0·94)	..
Topiramate	1·93 (0·76–1·15)	1·23 (0·99–1·51)

Figure 18 Time to 12-month remission for patients randomised to valproate, topiramate and lamotrigine (Marson et al 2007)

A number of critics of the SANAD studies have stated that carbamazepine was titrated to a high dose and therefore there were many drop outs with carbamazepine in arm A (French 2012). Also, the critics of SANAD state that it is not good evidence in particular for childhood epilepsies where the diagnosis of the epilepsy syndrome needs to be made meticulously.

In terms of adverse events, the SANAD studies were important as one of the outcomes was treatment failure and this provided a good comparative estimate of the risk of adverse events between drugs.

Overall the SANAD study is the largest trial to date informing clinicians on the cost benefits of treatments with one outcome for efficacy and one outcome for harms and a trade-offs made in the conclusions with the best drug for both partial and generalised seizures. In SANAD arm B, 36% of patients taking valproate and 45% of patients taking topiramate reported adverse events. These included psychiatric symptoms

related to topiramate and weight gain for valproate. Rash was the most common adverse event associated with treatment failure due to lamotrigine in arm B. The proportion of patients that withdrew due to rash was 4%. The proportion of patients with rash in arm A was 15% and proportion of patients with rash in arm B was 12%.

2.9 Trials of AEDs for other indications

Increasingly AEDs are used for the treatment of conditions other than epilepsy. These conditions can range from headache disorders, psychiatric conditions and peripheral nerve disorders. The reasons for this is due to the underlying mechanisms of some of the AEDs in blocking ion channels (Spina & Perugi 2004) Drugs such as carbamazepine have been used for trigeminal neuralgia and this was first used in 1962 by Blom (1962) and was only later undergone scrutiny with several RCTs (Killian & Fromm 1968) (Nicol 1969).

The list of possible conditions for which AEDs are used is extensive but can be broadly categorised as treatments for neuropathic pain, trigeminal neuralgia, migraine and essential tremor. Other uncommon indications are the use of AEDs in HIV related neuropathy and Guillian Barre Syndrome.

Psychiatric conditions where AEDs are used include bipolar disorder where carbamazepine, valproate and lamotrigine have mood stabilising effects (Bowden et al 2003). Valproate is considered one of the first line drugs for the treatment of acute mania and was found to be comparable to lithium.

The use of AEDs in other indications is important as RCTs in other indications may provide additional information on harms and is the topic of chapter nine.

2.10 Conclusion

In the past two decades, evidence based medicine has played a significant role in how treatments are evaluated. This is due to a cultural change in how doctors and patients interact with each other and a reduction in the importance of the clinical opinion in favour of judgments based on evidence. Tradition and clinical observations are no longer regarded as absolute truths in medicine and these have been replaced by the scientific method. Other factors that have facilitated the importance of evidence based medicine is the need for regulation of new products by regulatory authorities. This ensures the safety and efficacy of new treatments and helps regulators estimate the cost effectiveness of treatment.

The units of evidence-based medicine are composed of clinical trials, observational studies and other sources of evidence like case reports or case series. These units can be analysed into either narrative reviews or systematic reviews. Other types of evidence that can be used are health technology appraisals and guidelines. Various clinical trials reflect the tensions that exist between the needs of regulators and clinicians. Regulatory trials provide short-term results of efficacy to obtain a licence whereas clinicians need longer-term trials to demonstrate efficacy. One way to bridge this gap is to conduct systematic reviews that combine the results of several trials to produce a summary measure but these do not inform us of long term outcomes like seizure freedom or time to 12-month remission. Recently there has been collaboration between industry and local research bodies to fund large scale pragmatic studies like the SANAD study. The success of the SANAD study in demonstrating long term efficacy of lamotrigine in focal epilepsy and valproate in generalised and unclassified epilepsies has paved the way for a repeat of this large-scale study to include newer AEDs like levetiracetam and zonisamide (SANAD II protocol 2013).

Long term trials like SANAD have provided us with new outcomes like time to 12-month remission and time to treatment withdrawal. Secondary outcomes in the SANAD studies included adverse events and these were similar for lamotrigine in both arms A and B Such long term pragmatic trials are important as they reflect clinical practice and are of a longer duration that ordinary trials allowing for uncommon adverse events to be detected. The rates of rash for example in SANAD arm A and B

were similar (15% and 12% respectively), however the proportion of patients with rash in SANAD was higher than other RCTs of a shorter duration (Messenheimer et al 1998).

The current repository of harms data exists in several places ranging from regulatory databases, national databases, commercial databases, published randomised studies, observational studies and case reports. Each of these has strengths and weakness. The vast majority of this data is contained in randomised trials and observational studies and this may be mirrored in their corresponding databases. To date there are no studies comparing harms in RCTs versus observational studies.

Antiepileptic drugs are also used in other indications. The efficacy and safety of these AEDs in RCTs may be important in informing about harms.

The next chapter discusses adverse events, the corpus of knowledge regarding adverse events and adverse events in clinical trials of epilepsy.

Chapter 3

Harms due to Antiepileptic Drugs

3.1 Why study Adverse Events?

Epilepsy is a chronic disease and like any chronic disease there are many dimensions of the disease and its treatment that impact the patient. Patients with epilepsy face the burden of the physical and social consequences of seizures. Harms from seizures may occur during the ictal phase where patients can injury themselves or could die due to SUDEP. Harms can also occur during the inter-ictal phase and these comprise many of the psychosocial consequences of seizures. Harms due to adverse events are included in this category as conceptualised in the figure below. One can see that harms due to AEDs add to the burden of patients with epilepsy (fig 19).

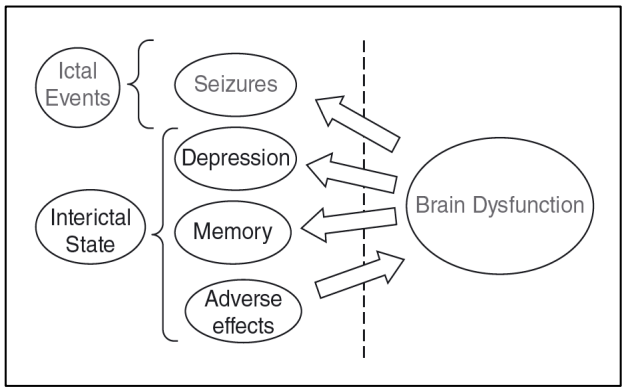


Figure 19 Conceptual framework of adverse events in relation to other co-morbidities in epilepsy

.

Epilepsy is routinely treated with antiepileptic drugs with a 60-70% chance of patients achieving seizure control (Kwan & Brodie 2000). One must remember that 60% of those patients who may become seizure free will still experience side effects. A European survey found that 88% of patients taking AEDs had at least one adverse event (Baker et al 1997). The proportion of patients that have discontinued a drug due to an adverse event on their first drug is about 10-27% (Kwan and Brodie 2000).

Patients can be treated as monotherapy, or polytherapy. Clinicians must balance the risk of harms of adding another AED and weight this up with the potential benefits of prescribing additional AEDs. One must consider that each additional AED prescribed to a patient may have a marginal benefit, as compared to potential side effects. A recent study by Kwan and Boride found that harms occurred in 12% of patients that were given add-on therapy and this when compared to patients who were prescribed

alternate monotherapy; they found that the latter group had a 26% chance of reporting adverse events. There was no difference in seizure outcomes between alternate mono-therapy and add-on therapy (Kwan & Brodie 2000).

Adverse drug reactions can differ from drug to drug and each drug can have its distinctive idiosyncratic drug reactions. However, many drugs still share common adverse drug reactions. It is accepted that the older AEDs cause more side effects than the newer drugs. The evidence that the older AEDs do not differ much between each other in terms of efficacy but differ considerably in terms of harms was noted in the Veterans studies of epilepsy in the late 1990s (Mattson et al 1996. The Veterans study of AEDs was published in 1997 and this was a head to head comparison. These studies were important in that they allocated treatment based on seizure types. For focal seizures, these studies showed no difference between AEDs. However, there were differences in AEDs in patients with generalised seizures. All the studies showed that AEDs differed in terms of adverse events (Mattson et al 1996). There is evidence to suggest that the newer AEDs are better tolerated due to their unique pharmacokinetics and pharmacodynamic interactions (Lee 2014).

3.2 Clinical importance of Adverse Events

Adverse events are a leading cause of failure of AED therapy. Adverse events can result in discontinuation of treatment in about 25% of patients (Lazaro et al 1998). According to the World Health Organisation, adverse drug events account for the sixth largest cause of mortality in the USA (Lazaro et al 1998). Adverse events can limit dose increases of AEDS leading to treatment failure and patients may not adhere to treatments for fear of adverse events.

Some methods of minimising adverse events include choosing a drug that is individualised to the patient. Rates of drug escalation should be slow to prevent dose related adverse events, this is particularly important when increasing lamotrigine in the presence of valproate (Messenheimer et al 1998).

Psychiatric adverse events are common with some AEDs. This is particularly true with levetiracetam; a study by Mula et al has shown that up to 10% of patients prescribed

levetiracetam develop psychiatric side effects (Mula et al 2003). This risk was increased slightly if there was a previous history of psychiatric disorder (Relative risk of 1.19 95% CI of 1.07 to 1.33). Antiepileptic drugs such as lamotrigine and valproate may conversely have mood stabilising effects and are useful in patients with psychiatric co-morbidities.

Some serious adverse drug reactions like Steven's Johnson syndrome due to carbamazepine can be predicted. Recent research has found two genetic variants of carbamazepine induced hypersensitivity reactions associated with HLA-B*15:02 and HLA-A*31:01 (McCormack et al 2011). Genetic testing of HLA-B*15:20 is recommended for patients with Asian ancestry. HLA-B*31:01 is common with this testing even though the positive predictive value of the test is low. The positive predictive value (PPV) of this in the Han Chinese population was estimated to be 7.7% and a negative predictive value (NPV) was estimated to be 100% (Ferrel & McLeod 2008). The PPV is low but due to the high morbidity and mortality of the adverse event, it would still be negligent if patients were not tested. If patients at risk are already taking carbamazepine for more than 3 months, they do not have to be tested (Amstutz et al 2014). Other efforts to find a genetic link to cognitive adverse events caused by topiramate have not found any association with ethnicity (Cirulli et al 2012).

Measures to manage adverse drug reaction in patients include careful monitoring, reducing dose when needed or drug discontinuation. Recent advances in genomic medicine may help predict the chances of harm in any patient before a drug is prescribed.

3.3 Definition of Adverse Events

Various bodies have defined this and these include the Food and Drug Administration, the World Health Organisation (WHO) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH). The first thing to clarify is the difference between adverse events and adverse drug reactions. These two bodies state that the term *adverse event* is not helpful for physicians and they prefer the term *adverse drug reaction*. The World Health Organisation defines adverse events as:

"..any noxious, unintended and undesired effect of a drug which occurs at a dose used in man for the prophylaxis , diagnosis or therapy" (WHO 2015)

The ICH defines adverse events as;
"..any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment"

On the contrary, it can be argued that the term adverse drug reaction may not be entirely appropriate as some harms can be due to excess dose related or but a predicable occurrence so the term adverse event is favoured in the medical literature. The relationship between adverse events and medical errors is linked in that some adverse events are due to medical errors but not all (fig 20). Bates et al formulated a conceptual framework on the relationship between adverse events, adverse drug reactions and medication errors this is shown in the figure below (Bates et al 1995). They also set definitions for the terms and definitions of levels of causality. This is shown in the table below (table 11). The terms harms and adverse events can be used synonymously.

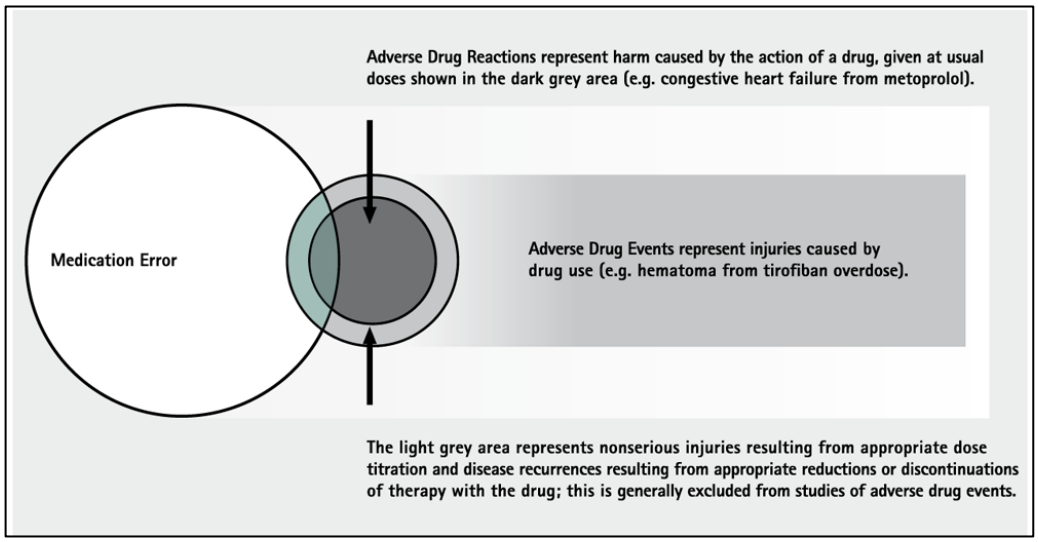


Figure 20 Relationship between adverse drug reactions, adverse events and medication errors: Adopted from Bates et al 1995

Adverse event and adverse drug reaction are regulatory terms; the first does not require a causal link between the drug and the events, the second does.

Adverse drug events extend beyond adverse drug reactions to include harms from overdoses and underdoses usually related to medication errors. A minority of adverse drug events are medication errors, and medication errors rarely result is adverse drug events.

The term side effect should be avoided

Table 11 Definition of adverse events and adverse reactions, grades of causal assessment of adverse events: Adopted from Nebeker et al 2004

3.4 Classification of Harms from AEDs

There are two commonly used ways of classifying adverse events: by cause or by severity. The Food and Drug Administration (FDA) prefers to classify adverse events by severity (Aronson 2002). In this thesis, adverse events will be presented by cause. The two main events to consider are type A and type B adverse drug reactions (table 12). Type A events constitute approximately 80% of all adverse drug reactions and they are consequences of pharmacological interactions or low therapeutic indices. Type A events are dose-related and usually mild in severity although they can be serious or fatal. Most type A events involve the central nervous system (Perucca & Meador 2005). Type B events are idiosyncratic events and these are those independent and unpredictable. Type A event can be acute in onset and resolution whereas type B reactions can be slow in onset and remit slowly.

Adverse Drug Reaction	**Description**
Type A	Augmented Pharmacologic events
Type B	Bizarre and Idiosyncratic
Type C	Chemical effects
Type D	Delayed effects
Type E	End of treatment effects
Type F	Failure of therapy
Type G	Genetic reactions
Type I	Idiosyncratic

Table 12 Classification of Adverse drug reactions. Adapted from Davidson's Principles and practice of medicine 19th edition

3.5 Pharmacodynamic and pharmacokinetic Adverse Events

Patients can vary in how they respond to antiepileptic drugs. Even when factors such as age and dose are controlled, the inter-patient variability of AED concentration can vary widely (Cloyd et al 1993). These are type A reactions. Pharmacodynamic interaction is when one drug alters the activity of another drug without a change in concentration. This can occur due to the interaction of one AED over the metabolism and protein binding of another AED. One example of this is the interaction of phenytoin and valproate. Phenytoin increases the metabolism of valproate and reducing its level if both are prescribed together.

Pharmacokinetic interactions are dose related and these can be either linear or non-linear. A linear response is when the serum concentration of drugs increases incrementally with dose increase and this can be predicted. Non–linear pharmacokinetics is when a unit change in dose can have an exponential increase serum concentration.

3.6 Adverse Events that affect seizures and epilepsy

Some adverse events can be due to an increase in seizures caused by antiepileptic drugs. This could be due to an increase in the number of seizures or a new seizure type developing. Types of seizures that typically occur due to AEDs are absence or myoclonic seizures. Drugs can precipitate seizures when prescribed in some situations. This typically occurs when carbamazepine, phenobarbital, vigabatrin and gabapentin are prescribed in patients with idiopathic generalised epilepsy. These would be considered as type A reactions as they are related to the AED interactions with ion channels. Other effects related to AEDs include psychosis and encephalopathy in association with valproate use and is dose related (Segura-Bruna et al 2006).

3.7 Life threatening adverse events

Most randomised controlled trials are conducted in the pre-marketing phase and therefore these trials at quite short in duration and are unlikely to report life-threatening adverse events. Adverse events from observational studies and reporting

agencies are more likely to report life-threatening adverse events. Life threatening adverse events can be either long-term adverse events, or idiosyncratic events.

An idiosyncratic drug reaction is one where the reaction cannot be predicted and happens uncommonly. They are also known as type B reactions. Cutaneous drug reactions could be thought of as an idiosyncratic drug reaction particularly if they occur late in treatment phase. Idiosyncratic drug reactions are a common source of morbidity and mortality. They account for 6-10% of all drug reactions (Pirmohamed & Park 1997). The vast majority of these reactions are due to AEDs. Adverse drug reactions can be described as being fatal and non-fatal. Non-fatal drug reactions are also associated with significant disability due to drug withdrawal. Life threatening adverse effects include serious rashes; aplastic anaemia due to felbamate and agranulocytosis due to carbamazepine. Drugs induced hepatic necrosis is another example of type B reactions that occurs with valproate and it occurs in every 26000 exposures. Similar to hepatotoxicity, valproate can cause pancreatitis that occurs one in 40000 cases.

3.8 Rashes from AEDs

Drug reactions due to rashes are common and can occur in 8% of patients, these can vary from morbilliform rashes to macular-papular eruptions. These are again type B or type I reactions. With regards to AEDs, these reactions occur with aromatic AEDs like phenytoin, phenobarbitone and carbamazepine. In most cases, the rashes are self-limiting and fade away after stopping the offending drug (Chadwick et al 1984). The aetiology of rashes is the result of an immunologic response to the drug and is therefore a type B reaction. Examples of this include rashes that occur with carbamazepine, and lamotrigine.

Severe drug reactions include Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia & Systemic Symptoms (DRESS) and Toxic epidermal necrolysis (TEN). Recent figures state that in the incidence of DRESS is 1 in 5000 patients taking carbamazepine (Arroyo & De La Morena 2001).

Genetic studies have demonstrated an association between hypersensitivity reactions and human leucocyte antigen HLA B*1502 in various Asian populations (Man et al 2007) (Metha et al 2009). This was first described by Chung et al in a case controlled analysis of HLA B*1502 (Chung et al 2004). This has been validated in numerous studies and since has led to an increasing scientific interest in the Food and Drug Administration updated the label for carbamazepine and recommends any patient of Asian background be tested for this allele before treatment. Mortality from these drug reactions can be high and recent efforts have led to the development of prognostic scores, which can predict mortality based on clinical features of the reaction (Bastuji-Garin et al 2000). Other risks factors for cutaneous skin reactions include; female gender; young age and having a learning disability (Alvestad et al 2007).

3.9 Cognitive Adverse Events from AEDs

All AEDs produce cognitive effects to some degree (Perucca & Meador 2005). Cognitive adverse events are the most common of all adverse events and can affect up to 60% of patients taking AEDs. (Gilliam et al 2004) (Baker et al 1997). Common cognitive effects of AEDs include concentration impairment and memory impairment. These are type A reactions. Older AEDs like phenobarbitone phenytoin and primidone are associated with cognitive side effects. Populations of patients that may have frequent cognitive side effects include the elderly and patients with learning disability. There is a suggestion that cognitive adverse events caused by topiramate may be genetically determined. Observational studies suggested that some ethnic groups are more likely to report side effects (Cirulli et al 2012). However, a genome wide association study did not find any association between ethnicity and cognitive side effects (Cirulli et al 2012).

3.10 Chronic Adverse Events

These adverse events are insidious but are significant in the long-term impact on the patient's quality of life. They are classified as type C or type D adverse events. Chronic adverse events include loss of bone mineral density caused by drug inducing AEDs, weight gain due to appetite stimulation due to sodium valproate, Polycystic Ovarian Syndrome caused by valproate, gingival hyperplasia due to phenytoin use and

barbiturate induced shoulder hand syndrome. Topiramate, felbamate and zonisamide on the other hand can cause long-term weight loss that can be reversible after stopping these AEDs. However, some of these type C events are not reversible and- an example of this is weight gain induced by valproate. Vigabatrin can cause insidious visual loss due to retinal degeneration (Perucca & Gilliam 2012).

Antiepileptic drugs pose a major teratogenic risk to the foetus when a pregnant mother has epilepsy takes medication at the time of conception or continues to do so during pregnancy. The risk is not solely related to major malformations but can have long lasting cognitive and developmental consequences on the baby (Shallcross et al 2014).

3.11 Reporting and assessment of harms in clinical trials

3.11.1 How is data on Adverse Events collected?

Source data for adverse events can vary from individual clinical trials to drug regulatory bodies. The collection of harms data in clinical trials is heterogeneous in the methods used. Some clinical trials use spontaneously reported adverse events whereas some clinical trials use validated tools for adverse events. The quality of reports is thus dependent on the methodology used in clinical trial (Perucca & Meador 2005). Some trials use spontaneous reporting of harms and other used a validated tool like the Liverpool Adverse Event Profile.

3.11.2 Clustering of Adverse Events: A new taxonomy

It is observed in clinical practice that some adverse events caused by AEDs may cluster in any given patient. A study by Perucca et al (2009) showed that 88% of patients in an outpatient cohort reported at least one adverse event and 82% reported two adverse events. They also found the mean number of adverse events per subject was 6.5. Certain adverse events can cluster in the same patients and the authors suggested that adverse events should be grouped into five classes these are illustrated in figures 21 to 22 on pages 60-61. These include; Cognition & coordination; sleep; skin & mucosal; mood & emotional and finally weight & cephalgia. This classification

is a significant step forward as taxonomy would allow for standardised recording of harms in a randomised controlled trial.

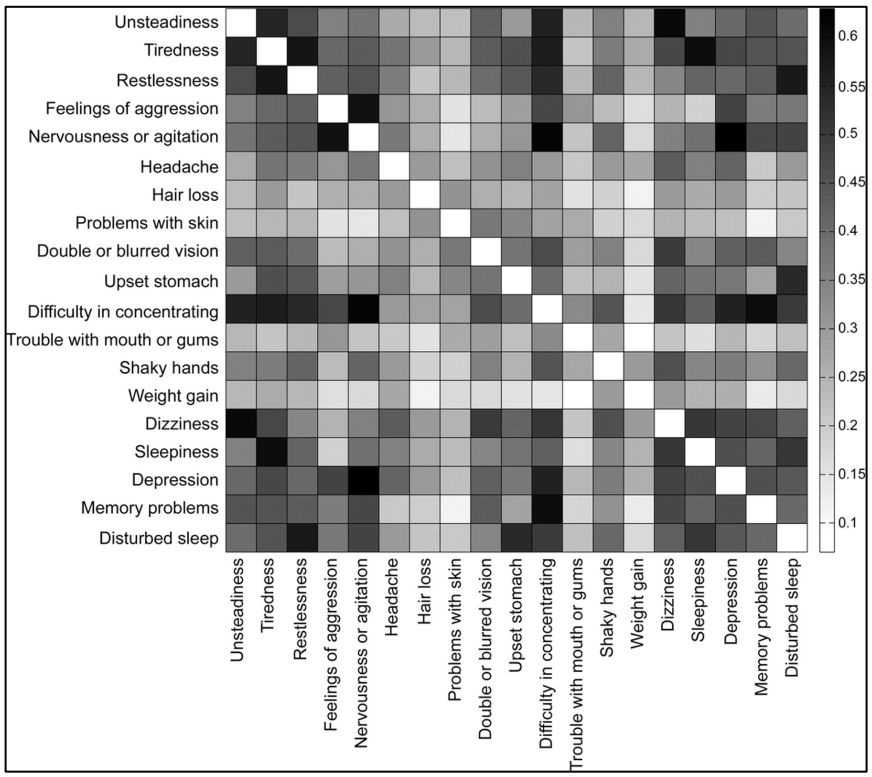


Figure 21 Correlation among the 19 adverse event profile items in LEAP in the entire cohort showing all correlations are significant except weight gain and hair loss (Perucca et al 2009)

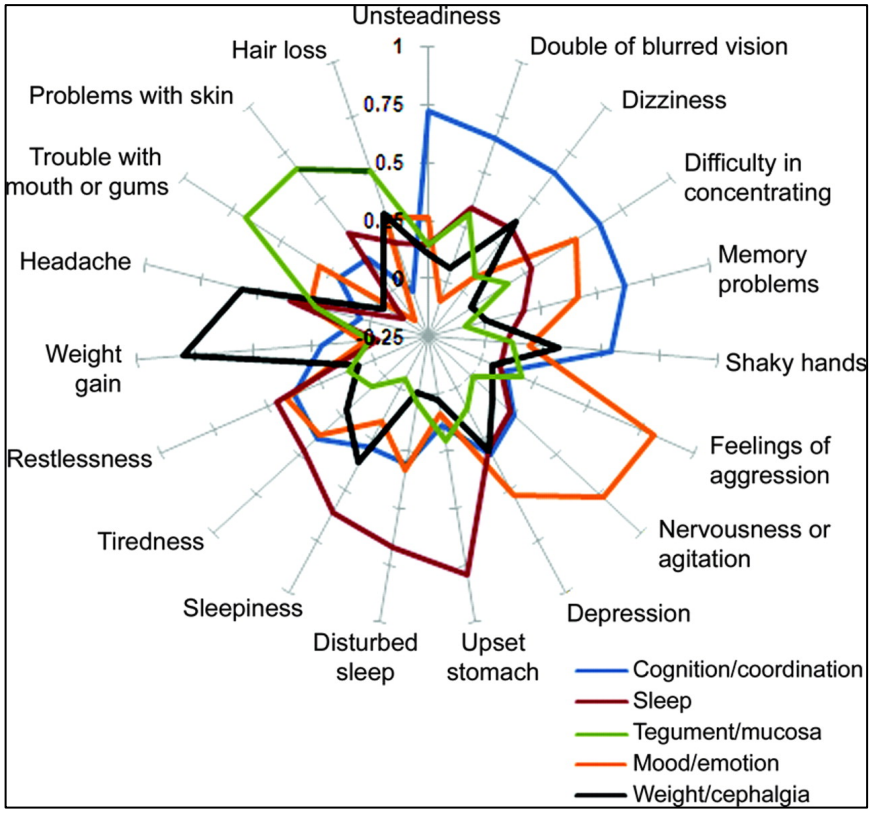


Figure 22 Radial plots illustrating the segregation of adverse events within each class as identified by factor analysis in entire cohort (Perucca et al 2009)

3.11.3 Adverse events in patients with newly diagnosed epilepsy: a comparison of treated and untreated patients

A recent study used the taxonomy for Adverse Events postulated by Perucca et al (2009). The authors created an adverse event profile (Perucca et al 2011). The Adverse Events Profile (AEP) is validated 19-item questionnaires that assess the frequency of the most common adverse events due to antiepileptic drugs. This is a questionnaire that is filled out by patients in clinic to provide a score of harms they may have experienced due to antiepileptic drugs. Scores of items ranged from 19 to 76.

A case controlled analysis of using the AEP was carried out in patients with new onset seizure. The patients compared of two groups, one group as treated immediately and another group was not treated. (Perucca et al 2011). They found that there was no difference in the AEP score and no difference in each of the six factor scores. This study suggested that in the newly treated population, there were no differences in the AEP score due to the low dose of AEDs. The authors suggested that of the 50% of

patients who become seizure free due to AEDs are not different to patients who are not treated with respect to adverse events.

This study is an important step, which elaborated on harms outcomes using two large datasets of patients with newly diagnosed epilepsy. This study demonstrated that useful data could be obtained from a clinical trial if the correct outcome measure is used. This study found that other factors influence AEP scores and therefore reporting of adverse events; these include young age of seizure onset; history of febrile seizures; symptomatic aetiology and female gender. The authors suggest that the history of febrile seizures reported more headaches and they hypothesised that this was due to sodium channel mutations that predispose patients to migraine (Perucca et al 2011).

3.11.4 Adverse Events reporting over time: Topiramate as a model

Most AE reported in RCTs mention the proportion of patients with adverse events and the proportion of patients withdrawn due to adverse events. There is little data in the time frame of adverse events. A recent study by Majkowski et al conducted post hoc analyses of data from topiramate trials. The authors plotted the time course of common CNS harms reported in a randomised placebo controlled trial of topiramate (fig 23, page 62). Patients were taking carbamazepine concomitantly as the first drug and topiramate was used as an add-on drug. Topiramate doses used in this trial do not reflect doses used in clinical practice as the studies used here have higher doses (dose range of topiramate was 200 to 1000mg per day whereas in clinical practice the doses are a lot lower).

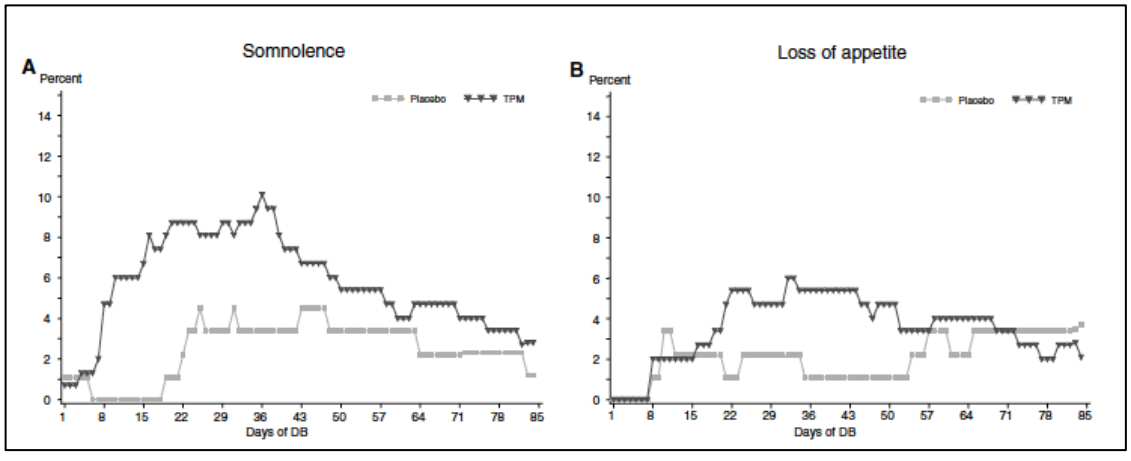


Figure 23 Incidence of somnolence and loss of appetite in a trial of topiramate versus placebo (Makkowski et al 2005)

The key outcomes were the total days in which patients had adverse events called AE days, the occurrence rate of AE which was the daily incidence of a given AE. They also calculated the AE time, which is the total number of days, divided by the number of subjects in that treatment group.

The results showed that common side effects occur at initiation of the drug and 80% of the side effects resolve after the 12 weeks of the double-blind period (figure 24) also the number of adverse events compared to placebo are the same after the titration period is over. However as one would expect, the number of patients with paraesthesia was higher in the topiramate group regardless of the phase of the trial. The incidence of weight loss also increases with time as would be expected (Majkowski et al 2005).

This study demonstrates an alternate method of analysing harms data and this will have implications on how Cochrane reviews handle harms data. However, this would involve a significant effort on drug sponsors and clinical trials to disclose more data.

Adverse events occur during the titration and maintenance phases but are more common in the titration phase. This trial provides a model of adverse events in plotting the incidence of harms over time rather than provide summary measures.

3.12 Observational studies of adverse events

Chapter two discusses the merits of RCTs and observational studies in relation to harms but the next section discusses this subject further.

There is no consensus to suggest that RTCs are better than observational studies when it comes to reporting of harms. Advantage of RCTs is that they are less prone to bias compared to observational studies. On the other hand, observational studies are cheaper and have a less restricted choice of patients for inclusion (Benson & Hartz 2000). Observational studies may have significant heterogeneity in harms measures therefore at this juncture we will limit ourselves to RCTs.

However, one of the largest studies to evaluate adverse events was a multicentre observational study (Cramer et al 2011). This compared newer and older AEDs in the

prevalence of each adverse event type. The primary outcome was the proportion of patients with greater than one adverse event and the prevalence of AE based on a rating scale called N&SAERS (Cramer et al 2011). A total of 1019 patients were recruited into this study. The results showed that overall 68.3 percent of patients reported one or more adverse event. Fifty eight percent of patients report one or more neurological adverse events and 40% of patients report one or more systemic adverse event. Patients are less likely to have adverse events if they were taking a newer AED compared with an older AED (odd ratio favouring newer AED was 0.64 with 95% CI of 0.46 to 0.89). Patients taking polytherapy reported more adverse events compared to monotherapy (odds ratio of 1.23 with 95% CI of 0.89 to 1.68). The results also showed that patients on AEDs are less likely to change treatments if the seizure occurred more than one year ago and this was related to fewer medical changes if patients were prescribed a new AED versus an older AED.

Some adverse events are noted to occur more often with specific AEDs. This type of data too is from large-scale observational studies. Examples of these adverse events include; headache associated with lamotrigine; depression with levetiracetam; anhydrosis and metabolic acidosis associated with AEDs that block carbonic anhydrase like topiramate and zonisamide (Brodie et al 2011).

Vigabatrin associated visual field defects were mentioned in chapter two. A review of observational studies by Maguire et al 2010 found significant heterogeneity in patients suffering visual field loss (Maguire et al 2010). Meta-regression to outline causes for this heterogeneity showed that dose and age were important predictors. Higher dose and increased age was associated with field loss. This study illustrated that for certain long-term harms outcomes like visual field defects, observational studies are better than RCTs in detecting these harms. However, they have significant heterogeneity that may need to be explored further.

3.13 “Placebo Drift”: a phenomenon just in AED trials?

The new AEDs when compared to older antiepileptic drugs (like phenytoin and phenobarbitone) has improved in efficacy. This is despite the phenomenon of a rising placebo effect in randomized controlled trials. This placebo effect is not just known in epilepsy but has been noted in various other conditions including gastrointestinal disorders, migraine, dementia, depression and Parkinson’s disease. There are several studies that have evaluated the placebo response in epilepsy (Schmidt et al 2013) (Rhimes et al 2008) (Burneo et al 2002). The most recent study by Guekht et al explored if there were any co-factors influencing this and if this was related to types of seizures and to examine if the phenomenon of placebo drift is still valid and current. The correlation between the placebo response rate and year of publication was linear with a Spearman’s correlation of 0.36 ($p = 0.064$) (Guekht et al 2010).

Placebo drift has implications for harms, as rising placebo effect that is noted in efficacy outcomes is not in parallel with a placebo effect when harms outcomes are compared (Guekhat et al 2010).

3.14 Conclusion

This chapter explored a number of issues pertaining to adverse events. Firstly, the definition of adverse events is difficult and adverse events include adverse drug reactions and other events that may not be directly related to the drug in question. This chapter also discussed adverse events and its relation to side effects and harms. The term side effect is a subset of the term adverse events. In this thesis, adverse events is defined using the WHO definition and the ICH definition. Both of these have their merits. The WHO definition gives us a broad view of what an adverse event is and the ICH definition is an operational definition for use in clinical trials.

There existed a need for the harmonisation of what harms are in relation to trials. This therefore has led to the creation of multiple validate dictionaries like World Health Organisation adverse reaction terminology (WHOART) and the medical dictionary for regulatory activities (MEDRA). Therefore, the collection of harms data may be harmonised and uniform across some trials, this does not mean that trials are reporting this data to an appropriate end consumer.

Adverse events in RCTs are common and some of these are dose related harms like dizziness, somnolence and fatigue amongst others. These are usually dose related and transient. Other adverse events are long term events like weight gain and bone mineral loss. Some AEDs have now been associated to specific adverse events like visual field loss related to vigabatrin and gum hypertrophy due to phenytoin (Pellock et al 2011). Transient adverse events may influence a patient's decision to continue with treatment or not and this can have significant consequences on their wellbeing.

A recent development is the discovery that some harms cluster together and these can be categorised into five major groups. The new taxonomy will allow a clumping of harms data collection in trial of AEDs and may produce more meaningful results. This could be used to replace existing dictionaries like WHOART and MEDRA. The advantages of a new taxonomy would be that terms which are synonymous like asthenia, fatigue and weakness may become obsolete. This would make clarify systemic reviews of harms and may allow for novel outcomes and tools for analysing harms in systemic reviews.

The study by Majkowski et al examined harms over the duration of the clinical trial and this found that harms commonly occur in the titration period of the study and that near the end of the trial these are no different to placebo. This raises questions on how harms data is collected in RCTs. This study provided a novel method in analysing and reporting harms (Majkowski et al 2005).

And finally harms form part of quality of life measure tools like the AEP (Perucca et al 2009). The use of the AEP in a recent trial has shown to increase the reporting of harm caused by AEDs and this has led to changes in dose or alteration of treatment regimens. A further study also showed that newly diagnosed patients with epilepsy if given AEDs do not have significant difference in side effects compared to those that are not treated. This is likely because they are started on low dose of AEDs (Perucca et al 2011).

The next chapter discusses the reporting of harms in randomised controlled trial and the CONSORT statements for harms.

Chapter 4

The CONSORT statements: Reporting of Adverse Events in Clinical Trials

4.1 Introduction

Harms caused by antiepileptic drugs are caused by common and cause significant morbidity and mortality. The previous chapter discussed the various types of harms caused by antiepileptic drugs. Data on harms can be obtained from either RCTs or observational studies. Our focus is on harms reported in RCTs, as these are the pivotal units used in systemic reviews over observational studies.

This section discusses evidence-based medicine and the reporting of RCTs, the reporting of harms in RCTs and the CONSORT statements.

4.2 Evidence Based Medicine

Current medical decisions are usually based on traditional teaching and pathophysiological understanding of the disease process. This method may still be the norm for some routinely made medical decisions, but clinicians may be faced with situations where information is from hard evidence such as clinical trials. This information is guided by evidence-based medicine (EBM).

Rosenberg and Donald introduced the concept of evidence-based medicine in 1995 to the research community (Rosenberg & Donald 1995) (Sackett et al 1996). They defined evidence-based medicine as a conscientious, explicit and judicious use of the best evidence in making decisions about the care of an individual patient. One must note that evidence based medicine does not entirely replace clinical experience, but clinical experience will raise questions and these can be refined, validated or refuted. EMB therefore supplements sound clinical practice. These also existed a gap between published research and how medicine was practised. Evidence based medicine therefore contributed to bridge the gap between research and applying the evidence into medical practice. There are gaps in the different direction of evidence and also the large number of trials that are published. The practice of evidence-based medicine can be summarised in four steps:

1) Formulate a clear clinical question from the patient's problem
2) Search the literature for relevant clinical articles

3) Evaluate (critically appraise) the evidence for its validity and usefulness
4) Implement useful findings in clinical practice

It is important to emphasise that evidence-based medicine is not synonymous with critical appraisal as the former combines research evidence with clinical skills, patients' values and preferences (Smith & Rennie 2014). The evolution of EMB has been such that there is more emphasis put into patients' values and this is reflected in how at least one peer reviewer needs to be a member of the lay public and a greater demand for reviews of pragmatic trials.

In this chapter evidence based medicine shall be discussed and how evidence based medicine (EBM) has contributed to the study of adverse events. Firstly, one is required to discuss the hierarchy of evidence.

4.3 History of the CONSORT Group

In 1993, a group of scientists spent four days in Ottawa to reassess the science of clinical trials methodology. The motivation for this meeting was to address and improve the reporting of randomised controlled trials in the medical literature. They developed a set of guiding principles on what constitutes a suitable trial report and published this in a document outlining the discussion of the meeting (Cook et al 1995). The guideline was developed by collaboration of the Standardized Reporting of Trials (SROT) group and the Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature. They drafted a consolidated guideline and called it the CONSORT statement. The original draft of the CONSORT statement was published in 1996 in JAMA and the BMJ (Begg et al 1996) (Altman 1996). The letters CONSORT stand for Consolidated Statement of Reporting of Trials.

The statements are available online from the CONSORT website and it is translated into eleven different languages (CONSORT 2010). Since their publication, the World Association of Medical Editors, International Committee of Medical Journal Editors (ICMJE) and the Council of Science Editors (Altman 2005) have endorsed these for instruction to authors. Subsequently there has been significant adoption of these statements by the medical press in general.

4.4 CONSORT Statements

It is a widely held notion that clinical trials are not reported adequately and this means that inadequate reporting leads to bias (Moher et al 2001). DerSimonian et al first made the original motion that editors could improve reporting in randomised controlled trials. They analysed four key journals for RCTs published between 1979 to 1980, the authors suggested that editors should provide a list of items that should be reported (DerSimonian et al 1982).

Since their inception in 1993, the CONSORT statements have undergone significant elaboration and revision. These revisions have sought to cover many aspects of randomised controlled trials. Following this the group has published several guidelines and these have been supplemented by providing extensions to current guidelines.
The original checklist of the CONSORT statement published in 1996 (Altman 1996) and was amended in May 1999. Table 1 shows the original checklist. This consisted of 22 items and a flow diagram. The changes made included: if authors used intention to treat analysis and a review flow diagram of clinical trials. It was envisaged that the CONSORT statements would eliminate poor reporting. The approach used in developing the guideline was not just by consensus of authors but in an evidence based manner. Authors were asked to provide some evidence if items included in the guidelines would improve reporting in RCTs. This approach in creating the guidelines also helped in the creating of other guidelines.

The updated guidelines of 2001 were also published with accompanying documents, which gave explanations and elaborations of the statements. The guidelines were updated in 2010 with elaboration and extension of the guidelines. These now are the current guidelines with nine extensions published separately.

The CONSORT website was established in order to identify which journal endorse the CONSORT guidelines. At the time of drafting this thesis, there are 585 journals that endorse the CONSORT statements. It is not just medical journals that have adopted the CONSORT statements, but they have been adopted by the nursing literature as well. (Smith et al 2008).

Many authors have used the CONSORT checklist as a benchmarking tool to generate a total score to compare individual trials. This score is used to summarise in some way the level of adherence to the CONSORT statements. This has been done a number of times using the original 22 item checklist. The table below shows items in the CONSORT checklist (table 13, page 73).

Heading	Subheading	Descriptor
Title		Identify the study as a randomised trial
Abstract		Use a structured format
Introduction		State prospectively defined hypothesis, clinical objectives, and planned subgroup or covariate analyses
Methods	Protocol	Plan study population, together with inclusion or exclusion criteria Planned interventions and their timing Primary and secondary outcome measure(s) and the minimum important differences and indicate how the target sample was projected Rationale and methods for statistical analyses, detailing main comparative analyses and whether they were completed on an intention to treat basis Prospectively defined stopping rules (if warranted)
	Assignment	Unit of randomisation (for example, individual, cluster geographic) Method used to generate the allocation schedule Method of allocation concealment and timing of assignment Method to separate the generator from the executor of assignment
	Masking (blinding)	Mechanism (e.g. capsules tablets) Similarity of treatment characteristics (for example, appearance, taste etc) Allocation schedule control (location of code during trial and when broken) Evidence of successful blinding among participants, person doing intervention, outcome assessors and data analysis
	Participant flow and follow up	Provide a trial profile summarising participant flow numbers and timing of randomisation assignment, interventions and measurements for each randomised group
	Analysis	State estimate effect of intervention on primary and secondary outcome measures, including a point estimate and measure of precision (confidence intervals) State results in absolute measures when feasible Presents summary data and appropriate descriptive and inferential statistics in sufficient detail to permit alternative analyses and replication Describe prognostic variables by treatment group and any attempt to adjust for them Describe protocol deviations from the study as planned together with reasons
Discussion		State interpretations of study, including sources of bias and internal validity and the discussion of external validity including quantitative measures when possible State general interpretation of the data in the light of totality of the available evidence

Table 13 CONSORT Checklist 1996, Items that should be included in reports of randomised trials: Reproduced from Begg et al 1996.

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4.5 Recent update of the CONSORT Statements 2010

The original CONSORT statement for parallel trials was published in 1996. It was revised in 2001 and updated in 2010. The aims of the guidelines are to offer guidance on how trials should be reported and they also provide guidance on how trials should be interpreted for quality. So the statements can serve as both a guideline and as a benchmarking tool. The new guidelines included some substantive changes. These changes include; addition of three times for registration of clinical trials or protocol and funding. Other sub items that were inserted were reporting if trials had any changes to methods after trial commencement and reasons for this, reasons for why the trial is stopped or ended.

4.6 Extensions of the CONSORT statements

The CONSORT statements provide guidance on standard parallel randomised controlled trials. However, there are other aspects of clinical trials that needed further elaboration. These extensions include areas of harms and other areas. The table below (table 14, page 75) shows the various extensions of the CONSORT statements produced.

Area	Reference	Description
Cluster trials	Campbell et al 2012	This updated the 2004 guidelines on cluster trials with updating on how abstracts are to be reported.
Non- Inferiority and Equivalence trials	Piaggio et al 2012	This updates the 2006 guideline on reporting of non-inferiority trials and equivalence trials. Specified items in methodology which indicated that the trials were a non-inferiority trial.
Pragmatic trials	Zwarenstein et al 2008	Older CONSORT items: background, participants, interventions, outcomes sample size blinding participant flow and generalisability of findings were extended and a new 22 item checklist was made for pragmatic trials
Herbal remedies	Gagnier et al 2006	Original recommendations were elaborated, including Latin and botanical names of interventions.
Non- Pharmacological treatments	Boutron et al 2008	Non-pharmacologic therapy includes surgical, medical devices, technical procedures
Conference Abstracts	Hopewell et al 2008	Journal abstracts may be the only piece of the article some readers may read. Therefore, this needs to be improved. A minimum set of criteria to help reporting in abstracts.
Patient reported outcomes	Calvert et al 2013	Patients reported outcome include those outcomes related to the quality of life
Harms	Ioannidis 2004	Emphasis for harms in 10 recommendations
Acupuncture	MacPherson 2010	This guideline elaborated on trials of acupuncture by providing 6 new items and 17 sub items
Allergen Specific immunology	Bousquet et al 2009	Not a true extension of the CONSORT statements but an adaption of the 1996 statement to immunology trials

Table 14 List of CONSORT extensions published to date

4.7 Harms research leading to the CONSORT extension for harms

The first paper to examine harms reporting was published as a letter to the Lancet in 1998. In this letter, Ioannidis and Ioannidis reviewed harms and toxicity of treatments for HIV-1 infection (Ioannidis & Contopoulos-Ioannidis 1998). In their review, they found that 87% of trials reported the proportion of patients withdrawn due to harms but only 38.3% of trials gave specify harms information for this. Definition of adverse events and toxicities were defined in some of the trials and only some trials discussed known validated toxicity scales. The authors concluded that the proportion of space used to list contributors of the article dwarfed the proportion of journal space for harms. The authors felt that similar work need to be replicated in other areas to highlight the deficiencies in harms reporting.

Consequent to the Lancet article on HIV infection, Ioannidis published a review in seven other areas of medicine including HIV infection in the journal JAMA (Ioannidis & Lau 2001). They found that similar results of poor reporting were found in trials of sinusitis, acute MI, arthritis, hypertension, helicobacter pylori and selective decontamination of the GI tract. Univariate analysis found that the odds of adequate reporting were higher if the trial was double blinded versus single blinded. Reporting was better if trials were larger and reporting improved over time. The authors discussed that their study highlighted deficiencies in reporting of harms and there needs to be an extension to the CONSORT statements to spread awareness of this issue.

4.8 CONSORT extension for Harms 2004

The original CONSORT statements contained only one item that mentions harms and due to this bias, an extension for harms was published (Ioannidis et al 2004). The paper fist defined that harms should be used instead of adverse events and a glossary of terminology was provided. They defined harms as:

> "The totality of possible adverse consequences of an intervention or therapy: they are the direct opposite of benefits against which they must be compared"

The CONSORT guidelines discuss the common poor reporting practises that occur with harms related data. Some of these are discussed in the recommendations but they are not all explicitly mentioned in the ten recommendations. A list of the poor practices and an elaboration of their meaning is shown in the table below (table 15).

Reporting Practice	Explanation
Using vague terms such as the" the drug was well tolerated"	Some trials will lack quantitative data on harms and may only report this qualitatively. The content of this however can be poor making it impossible to make comparisons between interventions
Failing to provide separate data	Important to allow comparisons between interventions
Providing summed numbers for all adverse events for each arm	Individual adverse events cannot be compared or analysed
Providing summed numbers of specific type of adverse events of the severity and seriousness of the events	Serious adverse events are not reported separately
Reporting adverse events that occur above a threshold or frequency	Only common and dose related adverse events are reported
Reporting adverse events that reach a significant P value	This it where trials report only significant outcomes
Reporting only measures of central tendency without indication on extreme values	Here only percentage of patients with harms without absolute values and confidence intervals
Not distinguishing between patients and one adverse event and participants with multiple adverse events	This stems for earlier errors where only the proportion of patients with adverse events are reported and not the absolute number of adverse events

Table 15 Common errors in harms reporting.

The statements proved ten recommendations pertaining to each section of the trial. They recommend that harms should be addressed, defined and analysed in each publication. The ten recommendations are associated with different sections of a publication. The first concerns the title of abstract; the second pertains to harms reporting in the introduction. Recommendations 3,4 and 5 are associated with the methods sections. Recommendation 6, 7, 8 and 9 are for the results section and recommendation 10 is related to the discussion section. Extracted items from the CONSORT statements are displayed below (table 16).

Section of paper	CONSORT Recommendation	Descriptor of CONSORT recommendations for harms	Items Evaluable
Title & Abstract	1	*If the study collected data on harms and benefits, the title or abstract should so state*	1 Adverse events mentioned in title or abstract
Introduction	2	*If the trial addresses both harms and benefits, the introduction should so state*	2 Information on harms mentioned in introduction
Methods	3	*List addresses adverse events with definitions for each (with attention, when relevant to grading expected vs. unexpected events, reference to standardised and validated definitions and descriptions of new definitions)*	3 Definition of AE mentioned 4 If article mentioned all or selected sample of AE 5 If article mentions treatment emergent AE (TEAE) 6 Use of validated instrument to report AE 7 Use of dictionaries for coding of AE
	4	*Clarify how harms related information is collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms related monitoring and stopping rules if pertinent)*	8 Description of how harms data were collected e.g. diaries, phone interviews or face-to-face interviews. 9 Description of when harms data were collected 10 Description of how adverse events were attributed to trial drugs
	5	*Describe any plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures and any statistical analysis)*	11 Description of methods for presenting and analysing harms in methods section. 12 Description of approach for the handling of recurrent events
Results	6	*Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment.*	13 Description of withdrawals due to harms in each arm. 14 Report contains data on serious adverse events and death.
	7	*Provides denominators for describing harms*	16 Provide denominators for harms 17 Provide definitions used for analysis set. 18 If trial states same analysis set used for efficacy and safety.
Results	8	*Present the absolute risk of each adverse event (specifying type, grade and seriousness per arm) and present appropriate metrics for recurrent events, continuous variables and scale variables whenever pertinent.*	18 Results presented separately for each group 19 Severity and grading of adverse events 20 Provide both number of events and number of patient with events.
	9	*Describe any subgroup analysis and exploratory analysis for harms*	Data not collected as very few trials conduct sub-group analysis
Discussion	10	*Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability and other sources of information on harms*	21 If prior literature is cited in the discussion in relation to adverse events. 22 If the discussion is balanced with regards to efficacy and harms. 23 If limitations of the study are discussed

Table 16 Extracted items from CONSORT extension for harms

4.9 Manuscript length

Manuscript length is an issue also discussed by the CONSORT statements. Adequate harms reporting need not make the manuscript excessively long. This apparent contradiction is negated by the assertion that if the methods and results sections are standardised, then there would be no need for long manuscripts Methods suggested to save space also include: publishing harms data in a separate article or in a webpage. Authors are also encouraged to give examples or case reports of serious adverse events in the discussion section.

4.10 Have the CONSORT statements made any difference to the reporting of randomised controlled trials?

One study compared RCTs published pre and post CONSORT using the 1996 statements (Moher et al 2001). The authors also compared the journals that were early adopters of the CONSORT statements (BMJ, JAMA and the Lancet) with a late adopter (NEJM). Their results show that after the CONSORT statements were published, there was an increase in the number of checklist items reported with a mean change in the number of items of 3.7 with a 95% CI of 2.1-5.3. This may seem like a modest increase in reporting but to the authors this was significant.

A similar study evaluated 98 articles across 4 nursing journals were benchmarked against the statements, the authors of this study found that the mean CONSORT score out of 48 was 24.7 with a range of 12-35 items. They also found that the quality of reporting did not improve from 2000 to 2005. They found that the items that were best reported included items from the title abstract, background and discussion (Smith et al 2008). These suggest that the reporting of harms overall is heterogeneous with poor reporting in some studies but adequate in others.

4.11 Systematic review of studies using the CONSORT statements

Plint et al conducted a systemic review of the studies that used the 2001 CONSORT statements in several areas of medicine (Plint et al 2006). They included eight studies that used the CONSORT checklist as a benchmarking tool. They extracted summary

measures of studies comparing trials adopting CONSORT and compared them to trials that do not adopt CONSORT (Plint et al 2006) see figure 24 below. They also extracted data on trials published before and after publication of the CONSORT statements. They concluded that CONSORT adopting journals are more likely to display data on sequence generation and participant flow and that the reporting of trials has consequently improved after publication of the CONSORT statements. This study is important because it was the first to quantitatively review some of the studies that used the CONSORT statement in their analysis. This has not been done for those studies that have used the CONSORT statements for harms but this was recently reviewed by Hodkinson et al (2013).

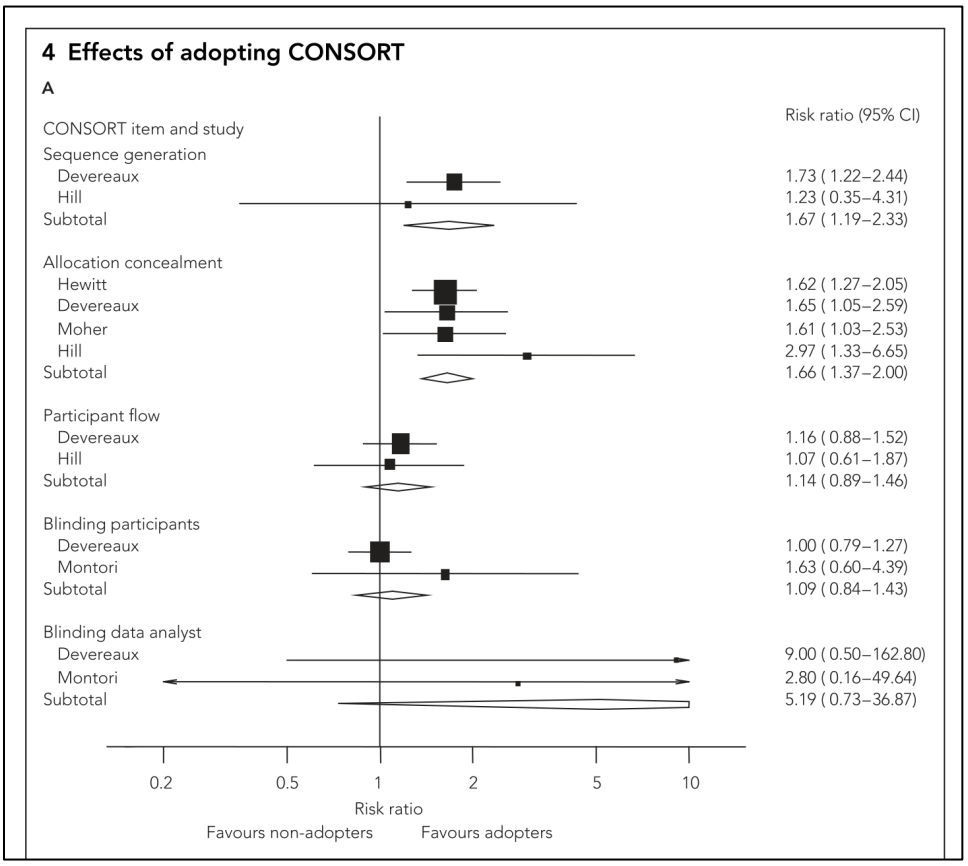


Figure 24 Analysis of CONSORT adopters compared to non-adopters: Data from five studies using CONSORT statements. This shows that CONSORT adopters analysed are better at reporting sequence generation and reporting, allocation concealments. But there was no difference with regards to participant flow and blinding (Plint et al 2001)

4.12 Endorsement of CONSORT statements by medical journals

There is evidence to suggest that the CONSORT studies have helped to improve the quality of RCTs. Here the authors tried to look at those journals that endorsed the CONSORT statements. A total of 167 journals were evaluated. Only 22% of journals mentioned the CONSORT statements in instruction to authors, this was worse in specialty journals (18% CW 22%). Only 43% of journals mention the ICMJE website but none of these provided a link to the ICMJE website (Altman D 2005).

4.13 Studies that have used the CONSORT statements as a benchmark: A qualitative review

This section qualitatively reviews all the studies that have used either CONSORT statements or the CONSORT extensions for harms. The aim is to summarise the data so far on the use of the statements as a benchmarking tool.

In the current literature, there are seventeen studies for inclusion after a search of the literature. Seven studies used the CONSORT 1996 guidelines. Two studies used the CONSORT extension for abstracts and eight studies used the CONSORT extension for harms. These are summarised in tables 17 to 19 for CONSORT guidelines and tables 20 to 22 for CONSORT guidelines on harms (pages 87 to 92).

4.13.1 CONSORT 1996/2001 guidelines & extension for abstracts

Nine studies evaluated the reporting of abstracts. These studies did not use the extension for harms but either the original CONSORT statements or an extension for abstracts. Studies were conducted in general medical and surgical journals but some were studies carried out in specialist areas ranging from paediatric trials, anaesthesiology trials, neurosurgical trials, and the dopamine agonist trials.

Two studies used the CONSORT extension for abstracts. One study by Bernal-Delgado & Fisher analysed 365 general medical journals and another study by Can et al analysed 527 abstracts form anaesthesiology journals (Bernal-Delgado & Fisher 2008) (Can et al 2011). Seven studies used the CONSORT 1996/2001 statements.

Only three out of nine studies carried out analyses of reporting pre and post CONSORT. Only one study compared commercially funded and non-commercially funded trials.

Each study used various items from the CONSORT statements, the use of items varied from study to study. The number of CONSORT checklist items used ranged from 11 items to 44 items.

Overall reporting of CONSORT items is poor. Two studies deemed that reporting has not changed since publication of CONSORT (Anttilla et al 2006 & Can et al 2011) whereas one study showed an improvement of 17 out of 22 items since publication of the CONSORT statement (Kane et al 2007).

Two studies compared general and specialty journals. Both of these studies found general medical journals were better than subspecialty journals (Mills et al 2005 and Kiehana et al 2011). Two studies compared CONSORT adopters versus non-adopters. Both found that CONSORT adopting journals are better at reporting items than non-adopters (Deveraux et al 2002) (Kane et al 2007).

4.13.2 CONSORT extension for harms 2004

Eight studies used the CONSORT harms extension as a benchmarking tool (see tables 20, 21 and 22 for references). Reporting of harms across studies and specialties. The percentage of trials reporting harm items ranged from 72% to 83%.

Four studies reported how withdrawals due to harms were reported. Withdrawal of patients due to harms was reported heterogeneously. Withdrawal data ranged from 25% of trials in one study to 70% in another. Five percent of trials reported harms in a supplementary webpage.

A comparison of commercial and non-commercial studies was conducted in two studies; both of these found that commercial studies were better at reporting harms than non-commercial studies. Two studies compared harms reporting pre and post CONSORT. Both studies did not find any change in harms post CONSORT.

Serious adverse events were reported in 20% of trials. A method of collection of harms was reported in 34% of trials. A table of adverse events was reported in 33% to 49% of trials. Twenty two percent of trials reported the severity of adverse events.

Reporting of harms in each arm also varied according to study. Percentage of studies reporting harms in each trial arm ranged from 27% to 87%.

4.14 Conclusion

The randomised controlled trial is the most important unit of evidence-based medicine. Here we discussed the development of the CONSORT statements and how they have been used as a quality assessment tool.

Reporting practices of journals with regard to randomised controlled trials were thought to be poor. This occurred during the time when academic institutions like the Cochrane group were reviewing how RCTs are used in systematic reviews. They noted that authors of RCTs have poor reporting practices and the evidence of poor reporting practices came to light after the authors carried out reviews of common drug interventions. Due to these concerns were raised in both sides of the Atlantic and change was needed. Due to these concerns, it was deemed that that change was needed to improve reporting. As a first step the need for highlighting inadequate reporting is needed.

In response to these issues, a collection of journal editors, statisticians and clinicians formulated the CONSORT statements whose primary aim was to inform trial authors on the minimum requirements expected for articles before they could be published. The secondary aims of the CONSORT statements were to serve as a tool to help readers critically appraise randomised controlled trials and to act as a quality assessment tool.

Poor reports of published trials carry a number of implications. The most obvious is that a poor report suggests that either the peer review process has been compromised or journal editors need to review their publishing practices. This therefore has implications on the validity of these trials. One cannot be sure if a trial is valid if the report of these trials did not mention key items such as allocation sequence and randomisation procedures.

Several studies have consistently shown that there is no change in the quality of reporting of trials since the publication of the CONSORT statement or its extensions. Journals that endorse the CONSORT statements are less likely to report RCTs poorly

compared to non-endorsers. This is probably due to the need for potential authors to format articles to conform to statements before they are accepted for publication.

Extensions of the statements have addressed issues of poor reporting and of these harms were a key area that needed review. The CONSORT statements for harms were published in 2004 and several authors have used it as a benchmarking tool. From these we learn that reporting of harms can vary with some trials reporting about 50% of items. Items are reported heterogeneously and this also varies by therapeutic area.

Eight studies outlined earlier used the CONSORT statements for reporting harms as a benchmark tool. It is not possible to summarise them quantitatively due to marked heterogeneity. These studies were selective in picking outcomes form the CONSORT statements making summation of outcomes difficult. Some studies like Breau et al found that reporting of harms in the urological literature is overall good but certain aspects of harms reporting of harms is poor (Breau et al 2010). Three studies compared commercial and non-commercial trials (Breau et al 2010) (De Vries et al 2010) (Faggion et al 2013). Two studies compared trials before and after the publication of the CONSORT statements (Breau et al 2010) (Faggion et al 2013). None of these studies examined antiepileptic drugs and this will be the focus of chapter six.

There are a number of questions that the extensions for the CONSORT statements raise. Firstly, one can argue that there are possibly too many statements now published. Authors may find it difficult to implement all of these. It is not possible a reader or author may be aware of all of these when writing his/her article. Secondly the statements are not adopted by journals that do not endorse these and the uptake of the statements should be encouraged. Journal websites should provide guidance using the statements on key items that would be desirable. The CONSORT statements should also be incorporated into the peer review process.

Specialty journal are unlikely to endorse the CONSORT statements. At the time of writing this thesis, a number of neurology sub-specialty journals do not endorse the CONSORT statements. Epilepsy is a specialty area. The potential for antiepileptic

drugs causing harms cannot be over stated. Clearly there is a need to assess the reporting of harms in epilepsy.

The next chapter discusses research methodology before a discussion of harms reporting in trials of AEDs.

Table 17 Studies using CONSORT guidelines.

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
Quality of Reporting of Randomized Controlled Trials in Cerebral palsy	Anttilla et al 2006	CONSORT 1996	Pediatric cerebral palsy	15	34	Yes	No	No	• Most trials reported items relating to introduction; participants in each group; and tables of results • Poor reporting of treatment allocation and methods of allocation generation • Only 50% of trials reported harms items • Pre & Post CONSORT no different in reporting
Abstracts in high Profile Journals often fail to report harm	Bernal-Delgado & Fisher 2008	CONSORT extension for abstracts 2008	Nil, RCTs chosen based on Journal impact factor	363	N/S	No	Yes	Yes	• Harms reported in 37.2% of abstracts • 9% of abstracts reported p-values for harms data • 53.5% of abstracts report harms in journal text and abstracts.46.5% report harms in journal text but not in abstracts • If harms outcomes are statistically significant, they are more likely to be reported in the abstract • Commercially funded abstracts more likely to report harms due to larger patient populations.
Has the quality of abstracts for RCTs improved since the release of the CONSORT guideline for abstract reporting? A survey of 4 high-profile anesthesia journals	Can et al 2011	CONSORT extension for abstracts 2008	Anesthesiology RCTs	527	16	Yes	No	Yes	• Items that improved post CONSORT in abstracts was blinding and adverse events (adverse events improved from 31.2 to 42.5% p 0.009) • Overall there was no change in reporting post CONSORT • Trial registrations are rarely reported • Quality of reporting is also predicted by the journal of publication • Word limits restrict reporting in abstracts.

Table 18 Studies using CONSORT guidelines.

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
Reporting in Randomized clinical trials improved after adoption of the CONSORT statement	Kane et al 2007	CONSORT 1996	Nil, Comparison of two journals one adopting and non-adopting	776	22	Yes	No	No	• Comparison made between JAMA which is a CONSORT adopter and NEJM which is a non-adopter • Seventeen out of 22 items analysed showed a significant increase in adherence to the statements post CONSORT • This was better in journal that adopted CONSORT and therefore adoption of the statements leads to improved reporting
Standards for reporting randomised controlled trials in neurosurgery	Kiehna et al 2011	CONSORT 1996	Five neurosurgical and three general medical journals	27	44	No	No	Yes	• CONSORT Score of a total of 44 was used • Comparison with general journals and sub-specialty journal showed that the general medical journal had a mean score of 41 and the sub-specialty journals scored 26.4 ($p < 0.0001$) • Journals which endorsed CONSORT had a higher impact factor
An Analysis of general medical and specialist journals that endorse CONSORT found that reporting was not enforced consistently	Mills et al 2005	CONSORT 1996	Comparison between general and specialist journals	200	11	No	No	No	• A comparison of 5 general journals and 10 specialty journals • General journal reported more items than specialist journals, mean score of 7.9 vs. 6.5 $p = 0.02$. • Odds ratio comparing the two groups for each item showed that four items out of 11 were statistically more reported in general journals than in specialist journals and these included; flow diagram OR 6.74; Sample size calculations OR 2.53 and sequence generation OR 2.9.

Table 19 Studies using CONSORT guidelines

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
The reporting of methodological factors in randomized controlled trials and the association with a journal policy to promote adherence to the CONSORT checklist	Devereaux et al 2002	CONSORT 1996	Comparison of general medical journal that do and don't endorse CONSORT	105	11	No	No	No	• Compared journals that do and do not endorse CONSORT on an 11 item checklist scale • Journals endorsing CONSORT report 6.0 items vs. 5.1 for journals that do not ($p = 0.03$). • 60% of all trials reported methods used to generate allocation sequence • Reporting of allocation sequence was 76% in CONSORT endorsing journals vs. 45% in those that don't ($p < 0.001$). • Details of blinding was reported better in CONSORT endorsing journals 46% vs. 22% ($p =0.001$)
Quality of Reports on Randomized controlled trials conducted in Japan: Evaluation of Adherence to the CONSORT statement	Uetani et al 2009	CONSORT 1996	Evaluation of RCTs published in Japan	98	29	No	No	No	• Reporting of trials conducted in Japan is poor • 39% of trials reported random sequence generation • 17% reported allocation concealment • Some items were reported better in CONSORT adopters versus non-adopters.
Randomsied Trials of Dopamine agonists in restless leg syndrome: A systematic Review, quality assessment and Meta-analsysis	Zintzaraz et al 2010	CONSORT 1996	Dopamine agonists	18	17	No	No	Yes	• Sequence generation was reported in 61% of trials • Allocation concealment was reported in 38.95 of trials • Participant flow was reported in 88.9% of trials • Adverse events were reported in 100% of trials

Table 20 Studies using CONSORT extension for Harms.

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
Reporting of Harm in Randomised controlled trial Published in the Urological Literature	Breau et al 2010	CONSORT extension for Harms 2004	Urology	152	16	Yes	Yes	Yes	• 72% of trial reported harms outcomes • No change in harms reporting pre and post CONSORT • 32% reported reason for withdrawal.22% reported severity of harms. 82% reported harms in title or abstract • Commercially funded trials met more harms criteria • 61.5% of trials mentioned harms in the discussion section
Endocrinology trial design: Adverse event reporting in randomised controlled trials of recombinant human GH in GH deficient adults	Bryant et al 2002	CONSORT addendum for harms 2001	Human Growth Hormone trials	17	N/S	No	No	Yes	• 29% of trial reported withdrawal due to adverse events • 59% reported results separately • 41% of trial reported the specific number of adverse events
Adverse event reporting in Acupuncture clinical trials focusing on pain	Capili et al 2010	CONSORT extension for Harms 2004	Acupuncture trials	10	12	No	No	Yes	• 70% of trial reported withdrawals • 60% of trials mentioned adverse events overall • 20% reported serious adverse events

Table 21 Studies using CONSORT extension for Harms.

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
Low quality of reporting adverse drug reactions in paediatric randomsied controlled trials	De Vries et al 2010	CONSORT extension for Harms 2004	Paediatric studies	107	15	No	Yes	Yes	• Created a CONSORT score of 5 points in total • 78% of trials mentioned adverse events • 25% of trials reported withdrawals due to harms • 65% of trials reported harms separately • Commercial trials scored 4.3 versus 2.7 for non-commercial studies ($p < 0.05$). • 33% of trials reported a table for harms data • 34% of trials reported a standard method for collecting harms data
Reporting of harms in randomized controlled trials evaluating stents for percutaneous coronary intervention	Ethgen et al 2009	CONSORT extension for Harms 2004	Coronary Stents	132	N/S	No	No	Yes	• 83% of trials described the nature of adverse events • 36% gave a definition of adverse events • 87% of trials reported harms separately • 14% of trials mentioned a data safety monitoring board • Provided mean percentage space for harms in each section of the trial report
The quality of Reporting Harms-Related Data in clinical trials of Adjuvant Trastuzumab in early-stage breast caner	Mahinbakht et al 2013	CONSORT extension for Harms 2004	Adjuvant Trastuzumab	5	10	No	No	Yes	• Analysed five trials using Trastuzumab • Adherence to CONSORT by section of papers was: Title and abstract was 40%; introduction was 60%; methods was 49%; results was 36% and discussion was 73%

Table 22 Studies using CONSORT extension for Harms.

Study	Author	Benchmark	Therapeutic area. Journals	Number of studies	Number of checklist items	Pre/Post CONSORT	Commercial/Non-commercial	Harms analysed?	Key Conclusions
Reporting of adverse events in randomised controlled trials in periodontology: A systematic review.	Faggion et al 2013	CONSORT extension for Harms 2004	Studies in Periodontology	246	10	Yes	Yes	Yes	• This study compared periodontal studies as a group of trials published between 2002-2003 with trials published between 2011-2012. • No significant change pre and post CONSORT except for mode of harms collection, denominators and subgroup analysis. • No difference in scores between commercially and non-commercially funded studies.
The Reporting of harms in randomised controlled trials of hypertension using the CONSORT criteria for harms	Bagul & Kirkham 2012	CONSORT extension for Harms 2004	Studies in Hypertension	107	24	No	No	Yes	• Mean CONSORT score out of 19 was 9.85 (95% CI of 8.06 to 11.6). • Reporting of items is heterogeneous • Only participant flow had reporting of > 50% • 49% of trial reported AE in a table • 29% of trials reported harms in each arm • 2 out of 41 studies (5%) provided harms information in a supplementary webpage.

Chapter 5

Evaluating harms in systematic reviews of randomised controlled trials

5.1 What is a systematic review?

Systematic reviews attempt to collate all the empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. The methods used aim to reduce bias (Altman 1996). Systematic reviews:

- Use a clearly stated set of objectives
- Are explicit and reproducible in their methodology
- Use search criteria seeks to identify all possible studies that meet eligibility criteria

The definition of a Systematic review is:
'A review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section.'

Meta-analysis is the use of statistical methods to summarise the results of independent studies to produce a single estimate of treatment effect. Not all systematic reviews include a meta-analysis. Systematic reviews should not be confused with narrative reviews where the selection of studies is not rigorous and smaller studies are excluded giving a biased opinion.

5.2 Why do Meta-analysis?

Clinicians may need information on the effectiveness of treatments for interventions. This information is usually obtained from several resources. This may be obtained from clinical trials, guidelines, case reports and conference meetings. Clinicians may find the plethora of sources of evidence daunting and these vary in grades of quality bias and scope. The best source of evidence of interventions is randomised controlled trials. However, RCTs may be prone to bias. The main aim of meta-analysis is to produce an unbiased and accurate estimate of the effect of a given intervention.

There are four key reasons to carry out a meta-analysis and these include:

1. To increase the power by combining trial there may be a statistically significant result which may be useful for clinical decision making
2. To improve precision of the treatment effect estimation
3. To answer questions not posed by individual studies. These can be done by examining subgroups from individual studies
4. To settle controversies from potentially conflicting studies

5.3 History of the Cochrane Collaboration

The Cochrane Collaboration is an international organization whose primary aim is to help people make well informed decisions about health care and preparing, maintaining and promoting the accessibility of systematic reviews of evidence (Higgins et al 2008).

The concept of the Cochrane Collaboration began with Archie Cochrane. He published a monograph "Effectiveness and Efficacy. Random reflexion on the Health Service" in 1972 (Cochrane 1973). This monograph was first published in book form in 1989. The electronic form of this forms the basis of the Pregnancy and Childbirth module of the Cochrane Library (Marson 2000). Subsequently this evolved into the National Perinatal Epidemiology Unit and after changing its remit. It evolved into the Cochrane Collaboration in 1992.

5.4 Cochrane Review Group

Systematic reviews are published in many journals. However, the Cochrane Collaboration is the leader in publishing quality reviews. The Cochrane Collaboration is consisting of groups of people from diverse medical fields that undertake and disseminate quality systematic reviews in its own area of interest. These groups collaborate with each other when needed. The number of different groups is large and each varies in size. These are called Collaborative Review Group; examples of these include the musculoskeletal disease, stroke, diabetes and epilepsy. All collaborative review groups have editorial teams and are answerable to a steering committee. Over the past three decades, the outputs of the review groups have been exponential in the

production of quality reviews. See figures 25 and 26 below. The review groups also maintain and develop software for producing systematic reviews. The latest version includes RevMan 5.0.

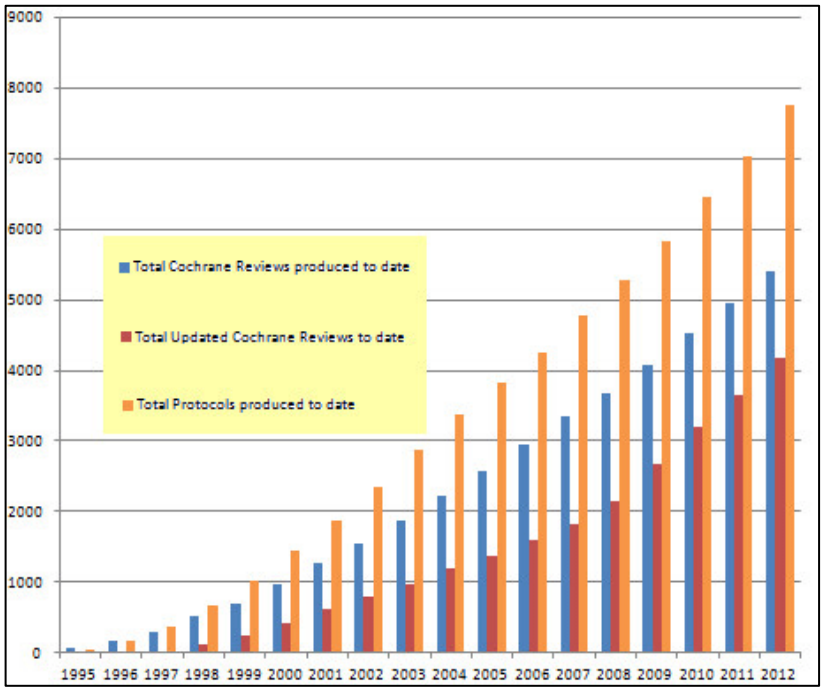


Figure 25 Growth of the number of systemic reviews produced by the Cochrane Group. Adapted from the ICHCA foundation webpage (2015).

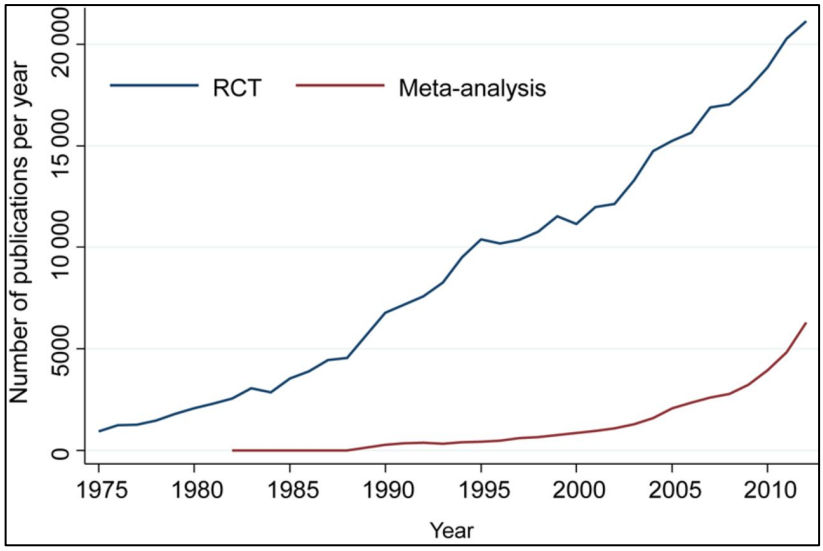


Figure 26 Growth of number of RCTs and meta-analysis indexed by PubMed. Adopted from Da Costa & Jüni 2014

5.5 The Cochrane Epilepsy Group

In January of 1996, a meeting was held in the Instituto de Mario Negri in Milan, to explore the possibility of setting up a Cochrane Epilepsy Group. Considerable enthusiasm was expected and following formal application the group was registered with the collaboration in September 1996. The editorial base for the group is in Liverpool UK, where staff includes a Review Group Coordinator, Assistant Review Group Coordinator and Coordinating Editors. The editorial base is currently funded by a grant from the NHS.

This scope of the group has been defined as follows:

‘. reviews randomized controlled trials and controlled clinical trials assessing the outcomes (including harms) of interventions that are designed to prevent and manage childhood and adulthood seizures and epilepsy.’

Much of the work focuses upon antiepileptic drugs however there are other interventions which are covered including the ketogenic diet, surgery, counselling, specialist nurses and clinics.

The editorial base has two main responsibilities. The first is processing a systematic review undertaken by members of the group. The editorial process of the group is outlined in the Groups Module on the Cochrane Library. In summary, the process starts with the registration of title and then the development of a protocol. The protocol is sent for external peer review, and then published on the Cochrane library. After completion of the review this is then published in the Cochrane Library. Each review should then be updated every 12 months.

At the time of writing, there are 85 published reviews and 24 published protocols (Cochrane Epilepsy Group 2015).

5.6 Systematic Review Methodology

Carefully conducted systematic reviews are essential to reduce bias. These are a series of steps that should be followed in creating a review. If the review is a Cochrane review then steps one to four form part of the protocol development stage.

1. Formulate and research/review question- this can be framed informally but this can be structured with subsections and have clear objectives. The research question is formulated by the PICO strategy as shown below.
2. Create a Protocol by using PICO and defining inclusion and exclusion criteria.
3. Define inclusion and exclusion criteria.
4. Identify studies and select studies.
5. Assess the study quality.
6. Extract the data from included studies.
7. Analyse and present the results.

5.7 PICO

The PICO strategy is a useful way of conceptualizing the research question. The acronym PICO stands for:

P- patient or problem
I- intervention of indications
C- Comparator
O- Outcome

This helps formulate separate parts of the question and refines it into a complete question.

5.8 What is a Systematic Review Protocol?

Given that a systematic review is a retrospective research study, a need to eliminate bias dictates that a protocol be created *a priori*. A protocol therefore reduces bias in the review. Protocols for a Cochrane review undergoes a peer-review process before the analysis occurs. The aim of this twofold: firstly, to help reduce bias and secondly as

part of the peer review process. Therefore, it is not surprising that Cochrane reviews when compared to industry-sponsored reviews are less biased in terms of results and in terms of methodological reporting (Jorgensen et al 2006).

Items included in a protocol are author's details and affiliation of the authors. Protocols will also include the methods used for selection of studies, selection of participants included in the studies and details of the interventions. Authors also include the background of the intervention and background of the clinical problem that is being studied. Protocol registration also stops duplication of systematic reviews. PROSPERO is an international database of prospectively registered systematic reviews in health and social care. The aim of this is to create a permanent record of protocol to prevent duplication. Registration of protocol also reduces bias by displaying any deviation from the protocol and the final published review. PROSPERO is based in York UK (University of York Centre for Reviews and Dissemination 2015).

5.9 Searches for studies

A valid systematic review would need to be backed up by a rigorous and unbiased search of studies. For this to occur the researcher has to be clear on the research question being asked, as this will affect the data needed for the summary estimate. Any loss of studies will introduce bias in a review.

The search for studies and decisions for inclusion and exclusion of studies involves electronic or hand searches. Given the availability of Internet and other technologies, the is use of hand searches have diminished, however single electronic searches are not enough as more trials can be included by other methods (Smith et al 1992).

Electronic searches are made via Medline and the Cochrane library. Here clinical trials are appropriately tagged as clinical trials, or randomised controlled trials. Searches in Medline will provide options for displaying only controlled trials. These tagged terms were only introduced in 1991. Therefore, trials before 1991 may not have been appropriately tagged.

Current tags include:

Clinical trial
Clinical trial phase 1
Clinical trial phase 2
Clinical trial phase 3
Clinical trial phase 4
Randomised clinical trial

Other search methods include searching for conference proceedings and contacting experts in the field. To further minimize bias two authors should search for trials independently for inclusion or exclusion.

5.10 Data extraction: How to choose outcomes from studies

Data extraction depends on the type of data and outcome. Majority of data in clinical trials is either continuous or binary. For the purposes of this thesis, I will restrict the discussion to binary variables. When outcomes are binary variables then treatment effect measures would include relative risks, odds ratios or risk differences. Examples of binary data are when there are two possible outcomes for a given patient. Outcomes would include if a particular event occurred or not or if there is clinical improvement or not.

5.11 Random Effects versus Fixed Effects Models

Models by their very nature are mathematical constructs with a series of assumptions to solve a given problem. When comparing effect sizes from randomised controlled trials there are two models used for meta-analysis, the fixed effects and the random effects model. The models were created to take account of heterogeneity in the analysis. In particular, it takes into account the different sizes of the studies in the model. Borenstein et al (2010) illustrates the two models as thus:

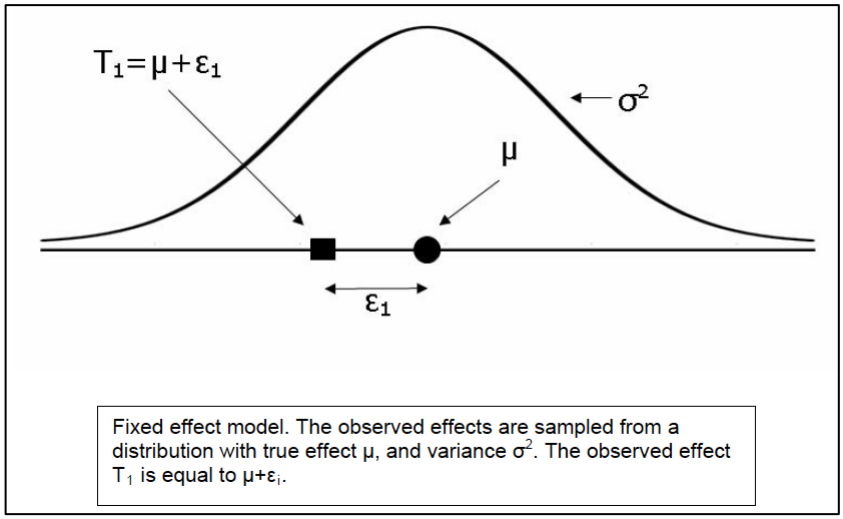


Figure 27 Fixed Effects model. Here all the studies share a common effect size represented by μ (Borenstein et al 2010).

In the Fixed effects model, all the studies are derived from the same population therefore they share the same common summary measure (fig 27). This effect is 'fixed' across studies. Here the effect size from each study estimate is a single common mean designated by μ.

In the random effects model each study has its own mean and the population distribution has its own variance (fig 28). Thus, the effect size has two components of variation and this is due to sampling error *and* due to variance in the underlying distribution. The mean is denoted by θ.

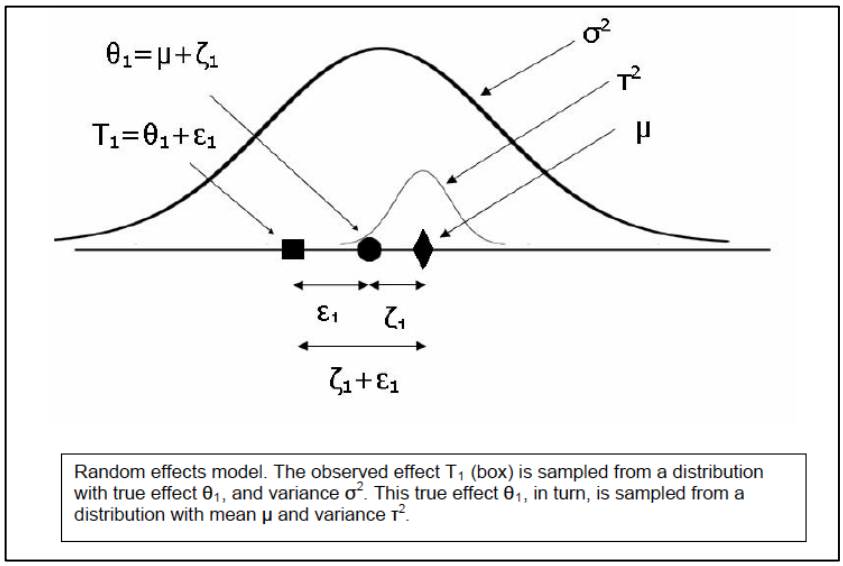


Figure 28 Random Effects Model. Here all studies don't have a common effect size because the studies are derived from different populations and therefore the common effect size is not one measure but a range of measures represented by the values between the mean value μ (Borenstein et al 2010).

A fixed effects model gives a more precise estimate of the summary effect whereas the random effects model provides a less precise result. Both models may give different estimates on the same set of studies and this is because of weighting.

5.11.1 How do weights affect the model?

Meta-analysis produces an average treatment effect pooled across multiple studies. Small studies may estimate treatment effects less precise than larger trials and this varying precision needs to be taken into account in the meta-analysis calculation. This can be achieved by weighting studies according to their precision, allocating greater weight to those studies that provide more precise estimates. The exact calculation of weight will depend on the meta-analysis method. For example, the inverse variance method assumes that the weight of the study is equal to the inverse of the variance. The pooling of the individual estimates has to undergo a weighting process where the weighted average is defined as the sum of estimates multiplied by the weights and is divided by the sums of the weights.

$$Weighted\ Average = \frac{sum\ of\ (estimate\ \times\ weight)}{sum\ of\ weights}$$

Therefore, statistical weight used in meta-analysis takes into account the statistical precision of each trial and gives more weight to larger trials in the fixed effects model.
In addition, we can make two different assumptions about the variability of treatment effects between studies. Firstly, a fixed effect model assumes that there is only one common treatment effect, which is estimated by each of the trials in the analysis. Any observed variation between the treatment effects is assumed to be due to sampling variation. This assumption can be examined using a test of heterogeneity. The alternative random effects model assumes that studies are estimating different underlying treatment effects that vary about a common effect. This therefore allows for heterogeneity between studies.

5.11.2 Which model should be used?

The choice between the random and the fixed effect models is based on how the effect sizes may vary between studies meta-analysed. This will of course depend on clinical

factors like types of patients across studies and on trial factors like how the allocation was carried out.

The two models therefore depend on different assumptions about the nature of variation among effect sizes. The fixed effect model should be used when studies are close replicates of one another and are using the same procedures and measures. The random effects model should be used when we anticipate variation in studies for a number of reasons.

5.12 Odds ratio versus Risk ratio

Dichotomous outcomes could be shown by arranging them into a 2X2 table this is able to calculate the odds ratio. The Mantel-Henszel is a method where by the odds ratios or relative risks can be pooled together. This method can be used for a fixed effects model. A 2x2 square is shown below:

	Outcome present	Outcome absent	Total
Risk Factor present	a	b	A+B
Risk Factor absent	c	d	C+D
	A+C	B+D	N

Risk ratio

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

Odds ratio

$$OR = \frac{a/b}{c/d} = \frac{ad}{bc}$$

There are two possible ways where binary outcome in systematic reviews are presented. The first is an odds ratio. An *odds* is defined as the number of patients who fulfil the criteria for a given endpoint divided by the number who do not. Risk is calculated as the number of patients meeting a endpoint divided by the total number of patients. Therefore, the odds ratio is the odds of the outcome in the intervention group compared to the control group.

Other ways of summarizing the relative effect for binary outcomes are Relative risks (also called risk ratios), risk difference and number needed to treat.

Risk ratio is the risk of an event in the experimental group divided by the risk in the control group. Odds ratio is the odds of an event in the experimental groups divided by the odds in the control group. If both ratios give a value of 1, then this means that there is no difference between the odds or risk of the event on experimental and control groups. The table below shows the various methods used for continuous and binary outcomes.

Type of Data	**Summary Statistic**	**Method (F: fixed effect, R: Random effects)**
Dichotomous	Odds ratio	Mantel-Haenszel (F) Peto (F) DerSimonian and Laird (R)
	Risk ratio	Mantel-Haenszel (F) DerSimonian and Laird (R)
	Risk difference	Mantel-Haenszel (F) DerSimonian and Laird (R)
Continuous	Weighted mean difference	Inverse Variance (F) DerSimonian and Laird (R)
	Standardized mean difference	Inverse Variance (F) DerSimonian and Laird (R)
Time to event	Odds/Hazard ratio	Peto (F)

Table 23 Summary of Meta-analysis methods available in RevMan 5.0

5.13 Displaying meta-analysis: Forest Plots

The results of a meta-analysis can be displayed as a forest plot. Here each treatment effect from a given trial can be displayed like branches of a tree. The horizontal lines represent the 95% confidence interval with the box showing the odds or risk ratio. The size of the box is proportional to the weight of the study in the meta-analysis. The diamond represents the pooled summary estimate and the width of the diamond corresponds to the confidence interval of the summary estimate or the overall effect. The vertical line represents unity of relative risk or odds ratio and if the horizontal line or domain touches the vertical line, it indicated that the confidence interval incudes unity.

The figure below (fig 29) shows forest plots of meta-analysis of intravenous magnesium with placebo on mortality in patients with acute myocardial infraction. Both fixed effects and random effects models are shown. The fixed effect model is dominated by the largest trial and the overall relative risk is 1.01 suggesting that there are no beneficial effects from magnesium on mortality. On the other hand, in the random effects model where individual trial weights are reduced the results show that intravenous magnesium has a beneficial effect on mortality. This has therefore changed the notion that magnesium is not beneficial (Da Costa & Jüni 2014).

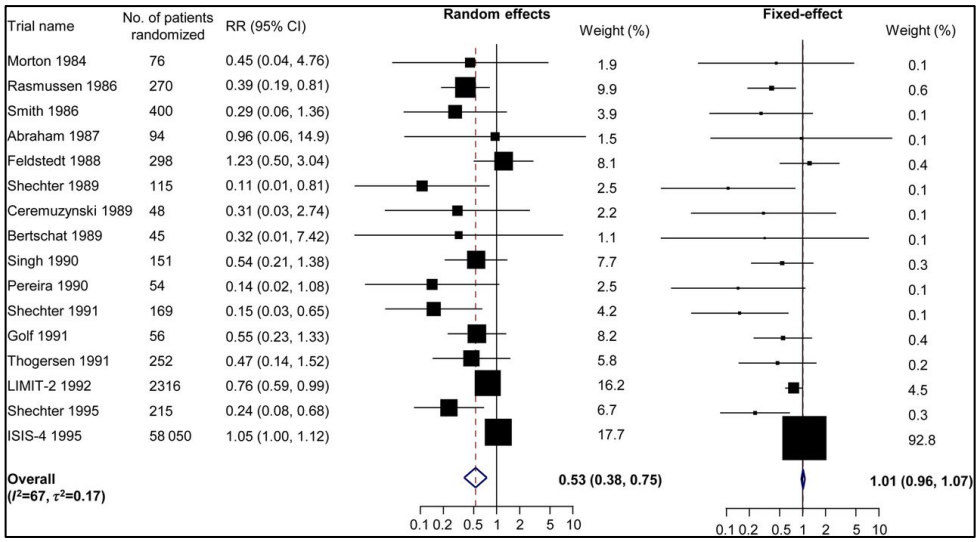


Figure 29 Mortality in patients treated with intravenous magnesium using random or fixed effects model (Da Costa & Jüni 2014).

5.14 Heterogeneity in systematic reviews

Meta-analysis combines to create a summary estimate. When trials are combined in this way it is possible that there may be heterogeneity between studies. Heterogeneity can be described as clinical, methodological, statistical or play of chance. A useful way of looking at heterogeneity is shown in the figure below (fig 30 page 106). Clinical heterogeneity is due to differences in patient characteristics or treatment regimens. Methodological heterogeneity is due to variations in study design or duration of follow-up. Statistical heterogeneity is true treatments effects across studies and finally the play of chance is due to uncontrollable factors.

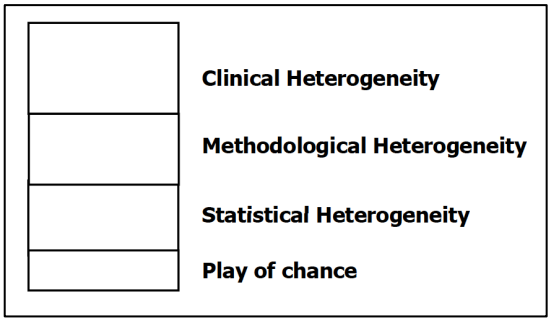


Figure 30 Spectrum of Heterogeneity.

Heterogeneity also depends on the number of studies evaluated, if a large number of studies are included, then heterogeneity may increase significantly. So large reviews with many studies might show a large variance in effect sizes and therefore show significant heterogeneity On the other hand a smaller review may show insignificant heterogeneity.

Recommendations for assessing, reporting and exploring heterogeneity was made by Pettiti in her paper in 2001 (Petitti DB 2001): the steps she described include:

1. Do a test of statistical heterogeneity
2. Report the results of the test statistic even if only qualitatively
3. State the p value used to reject the null hypothesis of homogeneity
4. State the rationale for using a fixed or random effects model based on consideration of the question addressed or alternatively do an analysis based on both random and fixed effects models and use this information for sensitivity
5. Where there is significant statistical heterogeneity then formally explore possible reasons for this

There are two ways of assessing heterogeneity in meta-analysis the first is the Q statistic and the next is the I^2 index. William Cochran developed the Q tests in 1950 (Cochran 1950). The Q test is calculated by summing the squared deviation of each study estimate from the overall effect estimate, weighting the contribution of each study by its inverse variance. A low p-value of the Q test means significant heterogeneous results among different studies. Usually a p-value at 0.10 is used as the cut-off. However, the Q test is not good to detect heterogeneity if there are few studies.

Another method used to quantify the degree of heterogeneity is the tau square statistic (τ^2). This measures the between study variance. If this > 1.0, this suggests significant statistical heterogeneity. A summary of how the tau squared and I^2 statistic are related is shown in figure 31.

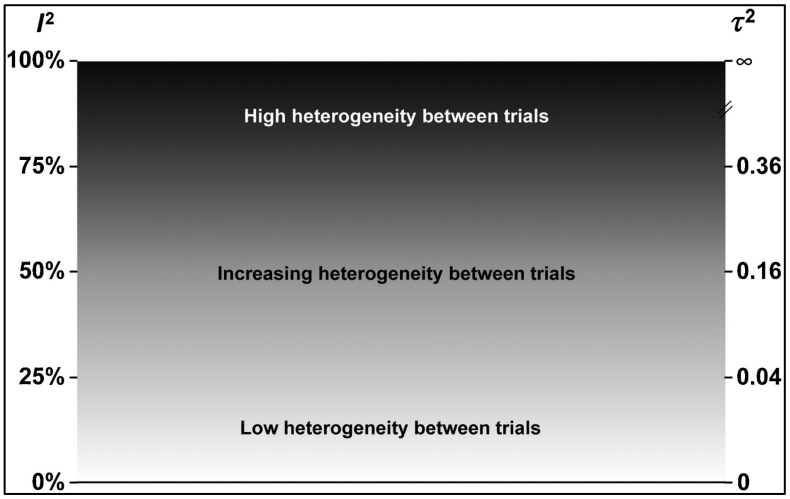


Figure 31 Interpretation of statistical Heterogeneity. Adapted from Da Costa & Jüni 2014

Formally, a statistical test of heterogeneity is found included in forest plots of Cochrane reviews. Higgins notes that statistical heterogeneity is inevitable in clinical trials due to methodological differences between trials and that clinical heterogeneity is due to the variation of true effects between studies (Higgins & Thompson 2002).

One method of quantifying heterogeneity is given by the I^2 statistic. It is calculated as:

$$I^2 = \left(\frac{Q-(k-1)}{Q}\right) \times 100\%$$

Where Q is the chi-squared statistic and k is the number of studies. Therefore (K-1) is also known as degrees of freedom. The I^2 is expressed as a percentage. The I^2 can range from 0 to 100%. To interpret the I^2 the original thresholds were changed and new threshold was published in the Cochrane handbook. They are shown below:

- 0% to 40%: might not be important
- 30% to 60% might represent moderate heterogeneity
- 50% to 60% may represent substantial heterogeneity
- 75% to 100%: represents considerable heterogeneity

An I^2 of 40% means that 40% of the observed variance is due to real heterogeneity and 60% of the variance is due to chance.

Q squared is a chi-squared statistic that is interpreted with the number of degrees of freedom. If the value of Q equals the number of degrees of freedom then the null hypothesis is true.

I^2 is a measure of inconsistencies in the effect sizes and reflects variances in effect sizes whereas Q squared is dependent on the precision of the trials An I^2 of 40% indicated that 40% of the observed variation is due to real heterogeneity and 60% is due to chance.

5.14.1 Clinical Heterogeneity

This is described as differences between trials that exist due to characteristics of the studies such as trial design, characteristics of study subjects such as age of patients, severity of illness and dose of interventions and duration of treatment. Clinical heterogeneity may therefore explain some of the statistical heterogeneity.

5.14.2 Investigating heterogeneity: Subgroup analysis

One method of investigating heterogeneity is by using subgroup analysis. Using this method, the analysis is conducted for a subset of patients or a subset of studies. using this method, we can observe if the Effect sizes change in degree or direction. If the effect changes in direction from beneficial in one subgroup to harmful in another, then this is called a qualitative interaction. If the effect changes in magnitude between subgroups and not direction then this is a qualitative interaction (Yusuf 1991). Another method to explore heterogeneity is to use meta-regression.

5.14.3 Meta-regression and dealing with heterogeneity

Meta-regression is like simple regression where the outcome variable is predicted according to the values of one or more explanatory variables. Meta-regression was first used by Berkey et al to investigate the effect of latitude on the effectiveness of the BCG vaccine for tuberculosis (Berkley et al 1995). The initial use of meta-regression was to explore heterogeneity but recent use of meta-regression is to explore the effects of covariates and provide a clearer interpretation of the effects of covariates to the study outcome.

A minimum of ten studies is needed to carry out a meta-regression. If the studies selected for meta-regression have patients obtained for the sample population then the fixed effects model should be used as it is expected that there is a common treatment effect. If the populations are heterogeneous then a random effects model is used. Under the fixed effect model, a common effect size is calculated and under the random effects model, a mean of the effect sizes is calculated. In addition, under the fixed effects model, larger studies have a greater effect on the effect size but in the random effects model the relative weights are the same.

In simplistic terms, a regression equation is a modification of the equation:

$$y = ab + x$$

Where y is the outcome, x is the intercept and a is the exploratory variable.
The regression equation is elaborated into:

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n + \varepsilon$$

Where y is the dependent variable, β_0 is the regression intercept, x is the exploratory variable and this is used to predict the dependent variable y.
β is the regression coefficient and β_0 is the intercept and ε is the residual.

The outcome variable y is the effect estimate and is usually computed into a log risk or log odds ratio. The explanatory variable is some other variable or characteristics of the study that might influence the effect size. Explanatory variables can be continuous or categorical. If they are continuous then a regression equation can be calculated. If the exploratory variables are categorical then the regression line/lines is the mean of the log of effect sizes. Then if the intercept is not zero then this could be a residual or β_0. Both the intercept and residuals can be calculated using relevant software.

5.14.4 Meta-regression software

Consider figure 32 on page 111. The top panel illustrates all the possible data from a number of studies that could be plotted on a regression line. To do this, we can plot the dependent variable on the y-axis and the covariates on the x-axis and then plot a regression line. New software (CMA version 3.0) can plot the covariates as either continuous variables or categorical variables. The figure illustrates that data spilt into hot or cold as categorical variables in the bottom left panel or as a continuous variable as shown in the bottom right panel.

In the first case, the regression line is the mean of the effect sizes for each of the groups. The mean of each group is the intercept also. The variance of the data in each category can also be obtained. The variance of each of the categories can be compared to the variance of all the data and this will give us an estimate of how much of the variance can be explained by the model and how much of the variance is due to random error. These can be expressed as a ratio to quantify how much of the variance is explained by the model when covariates are plotted on a regression line.

One can calculate the p-value of how much of the model explains the data, the p-value of the goodness of fit of the variables on the regression line and we can calculate the intercept. This method of meta-regression shall be used in the final chapter.

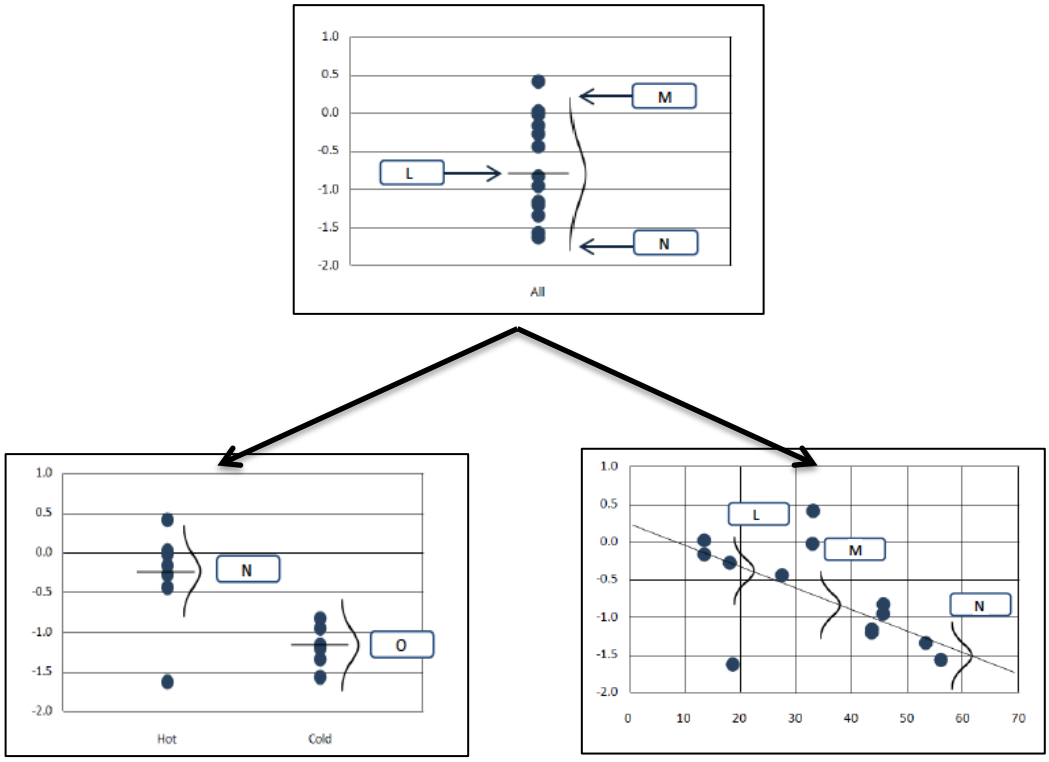


Figure 32 Data before and after meta-regression. The figure on the left is where data is plotted using categorical covariates and on the right, is using continuous covariates. Note that in both models the variance of data decreases when data is plotted against a regression line (Bornstein et. Al 2010)

5.15 Improving the quality of reporting of Meta-analysis: QUOROM statement

As stated earlier, the results of the meta-analysis can be flawed for a number of varied reasons. A discordant meta-analysis in a review occurs when the methodology of reviews is poor, producing summary estimates that are clinically misleading. Le-Lorier et al evaluated the issue of discordant meta-analyses. They compared and contrasted summary measures from a sample of RCTs and their corresponding systematic review in the Cochrane database. They found that in 33% of cases the meta-analysis have led to the adoption of ineffective treatments and in 32% of cases the meta-analyses has found an ineffective treatment to be effective (Le Lorier et al 1997).

Given the importance clinicians place on systematic reviews and meta-analysis, the need to assess the quality of systematic reviews became important. The QUOROM statement was established to address this issue. The QUOROM statement is an 18-point checklist. Similar to the CONSORT checklist, the QUOROM statement seeks to improve the reporting and production of reviews (Moher et al 1999).

5.16 Bias in clinical trials

Trials with inadequate allocation concealment or lack of blinding may exaggerate the estimates of intervention effects. However, this is not shown in all studies and may vary based on the design of the study. Flaws in the conduct of randomized controlled trials such as allocation concealment and lack of blinding may introduce bias to the results, which may lead to exaggerated results of estimates of effects of interventions (Wood et al 2008).

One method to reduce the risk of bias is to use tools and methods suggested by the Cochrane Collaboration. They identify six domains of clinical trial conduct and they include:

1) Sequence generation
2) Allocation concealment
3) Blinding of participants
4) Incomplete outcome data
5) Selective reporting
6) Other factors

Higgins at al describe several sources of bias in clinical trials A list of items were described in his seminal paper, a summary of which is shown in the table 24 on page 113 (Higgins et al 2008)(Higgins et al 2011).

Bias Domain	Source of bias	Support for Judgment
Selection bias	Random sequence generation	Describe the method for allocation sequence in sufficient detail to allow whether should produce comparable groups
Selection bias-	Allocation concealment	As above
Performance bias	Blinding of participants and personnel	Describe all measures used to blind trial participants and researches from interventions a participant received
Detection bias	Blinding of outcome assessment	Describe all measures used if any to blind outcome assessment
Attrition bias	Incomplete outcome data for each outcome	Describe completeness of outcome data for each main outcome including attrition and exclusion s from analysis
Reporting bias	Selective reporting	State how selective outcome reporting was examine and what was found
Other bias	Any other Bias	State any other important sources of bias not described earlier

Table 24 Cochrane collaboration tool on assessing the risk of bias from Higgins et al 2011.

Authors are then asked to make summary assessments of the risk of bias for each individual item or outcome and this is categorized into low risk unclear risk of bias or high risk of bias. The risk of bias is then shown in a figure, an example of which is shown below (fig 33).

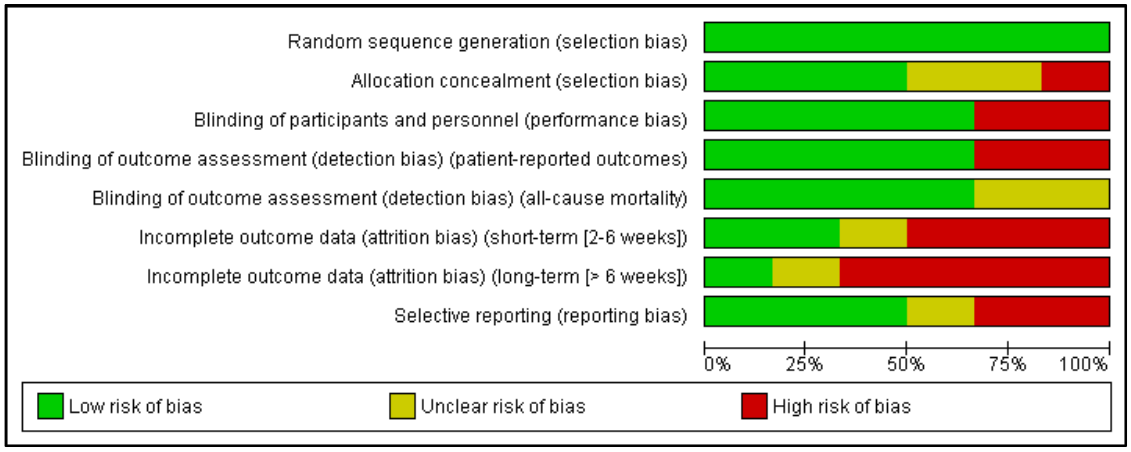


Figure 33 Example of risk of bias tool used in systematic reviews

Another similar form of outcome reporting bias is called the “tower of babel bias” here only those trials which are in English are included in systematic reviews and therefore any potential negative study will not affect the outcome (Grégoire et al 1995). It has been estimated that English only meta-analyses may overestimate the treatment effect by 2% (Moher et al 1998).

5.16.1 Outcome reporting bias: the ORBIT tool

Published studies are more likely to contain results that are statistically significant than unpublished studies. In addition, many studies have outcomes that are analysed but are not reported. It is estimated that between 42 -60% of trials changed, introduced or omitted at least one primary outcome (Dwan et al 2008). Outcome reporting bias can affect systematic review when some studies that are not statically significant are not published at all or if they are published then not all measures outcomes are reported. This incomplete reporting leads to reporting bias. This bias may affect systematic reviews as if only those outcomes that are significant are reported the effects of that outcome may be additive when meta-analysed and if other outcome were used, it might have had an impact of the outcome. Outcome reporting bias is not only restricted to RCTs but is also seen in systematic reviews. There is evidence that some meta-analyses that are not statistically significant are not published (Moher et al 1999). Systematic reviews by their very nature will amplify effect sizes. This happens because if non-significant studies are not reported or analyses will not distort a summary measure whose confidence interval is increasingly getting smaller. Estimates of how much outcome reporting bias may affect estimates has been determined to overestimate outcomes by 12% (McAuley et al 2000). Measures developed to reduce outcome-reporting bias include mandatory registration of trials in www.clinicaltrials.gov with publication of all planned outcomes in protocol before publication of the clinical trial results.

5.17 Other limitations to Cochrane systematic reviews

Mark Wilson the CEO of the Cochrane collaboration discusses the limitation of the Cochrane systematic review process (Wilson 2014). Some of these include:

1. Reviews are not focused on key issues of the day, they are focused on the reviewer and not the end user.
2. Are inflexible
3. The emphasis on randomised trials only limits other sources of evidence like observational studies and therefore the Cochrane group need to develop other tools for these
4. Cochrane centre gives the impression of an exclusive club
5. Limited awareness outside academic circles

In its strategy document, the Cochrane Collaboration aims to produce other forms of evidence apart from the current systematic reviews. They however have not explicitly divulged what this might be. The strategy also aims to explore new mobile technologies like iPads and iPhones and therefore create "softer" versions of its database for mobile and use by non-academics. (2014, Cochrane Strategy to 2020).

5.18 Conclusion

Systematic reviews are structured documents with a protocol stage followed by an initial peer-review of the protocol. This is followed by a formulation of the documents and a second peer-review stage before publication. In this way, any potential bias in selection of studies and biases in data extraction is reduced. Other means of reducing bias is blinding when data is extracted from clinical trials. Trials are meticulously analysed to reveal any biases in methodology and these are displayed in a standard format approved by the Cochrane Collaboration. Software provided by the Cochrane collaboration allows for the publication of quality reviews with the option of including meta-analysis software, which is free of charge.

This chapter focused on the statistics behind meta-analysis. Concepts and methodologies described here will be used in chapters to come. The aims and objectives of the remaining chapters are:

- To evaluate CONSORT adherence on reporting harms in RCTs of AEDs
- To explore the impact of reporting standards on the conductance of systematic reviews of AEDs
- To explore the utility of using lacosamide trials for different indications in enhancing the accuracy of information about harms
- To explore utility of using meta-regression techniques of other AED trials for different indications on informing about harms

Chapter 6

Reporting of harms in randomised controlled trial of antiepileptic drugs

6.1 INTRODUCTION

The primary outcomes of RCTs are measures of benefits and secondary outcomes include a mixture of benefits and/or harms outcomes. Harms outcomes usually included common adverse events as RCTs only can report events that occur for the duration of the clinical trial. RCTs therefore may not be the best method to assess harms outcomes of interventions and these are better reported in observational studies. These studies have a longer duration in comparison to RCTs but they lack a placebo arm therefore making a judgment of relative risks impossible. Therefore, RCTs are able to compare harms between interventions and placebo, which allows informed decision making regarding risks and benefits.

Informed treatment decisions are important for chronic interventions for conditions such as epilepsy as the treatment may be taken for many years. Adverse events of antiepileptic drugs can have lifelong effects with a significant impact on quality of life and patients and doctors need to have an informed discussion about the potential risks and benefits of AEDs. Patients also are more informed of the likelihood of a drug having long-term effects and commonly ask about adverse events.

There is a growing consensus that reporting of adverse events in randomised controlled trials is not adequate (Breau et al 2010) (Bagul &Kirkham 2012) (Faggion et al 2013). This issue has been discussed in several forums by clinicians and trial methodologists alike. To address this issue, the CONSORT group outlined a guideline and a checklist of minimum standard of adverse event reporting in RCTs. Several studies have used the CONSORT checklist as a benchmark to report on the quality of adverse events reporting; however there have been no studies to establish this in trials of AEDs. In this section, I will discuss the reporting of adverse events in randomised controlled trials of antiepileptic drugs.

6.2 AIMS

The aims of the chapter are to:

- Report the quality of reporting of adverse events in RCTs using the extension of CONSORT statements pertaining to harms.
- Secondary aims are
    a. To compare the quality of trials
        i. Funded by industry vs. not funded by industry
        ii. Trials recruiting adults vs. those recruiting children
        iii. Trials published before and after the publication of the amended CONSORT guidelines of 2004
        iv. Trials published in epilepsy and non-epilepsy journals
        v. Trials published in speciality and non-specialty journals
        vi. Other outcomes stated in the CONSORT statements for harms

6.3 METHODS

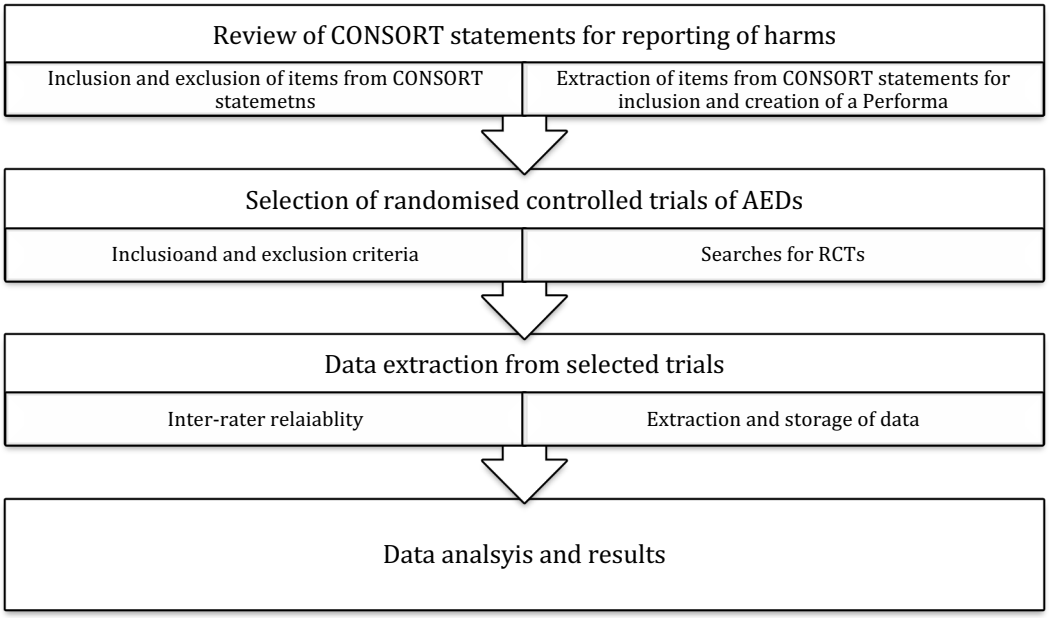
6.3.1 Eligibility and identification of studies

This review analysed randomised controlled trials of anti-epileptic drugs for this review. A brief outline of the process is shown below. The first task involved outlining the inclusion and exclusion criteria. Once this was defined, one reviewer carried out searches for the remainder of the trials. However, to ensure reproducibility of searches, a comparison between two researchers was made; if there was good agreement between researchers, all trials were searched by one reviewer.

Data extraction from clinical trials had to be reproducible and this was assessed by inter-rater agreement statistics. To ensure the quality of the data extraction process, two reviewers carried out inter-rater comparison. Following this, one reviewer extracted data from the remainder of the trials.

The CONSORT statement had to be analysed to create an operational checklist. This is needed to include all possible items that could be audited. Next the data from clinical trials were extracted for further analysis.

The analysis stage involved a number of processes, which included comparison of mean scores across all trials, analysis of mean scores amongst subgroups of trials and lastly analysis of individual CONSORT items in the trial population.



6.3.2 Inclusion and exclusion criteria

To be included trials would need to have been published between January 1999 and December 2008 inclusive. This interval period was used because the CONSORT criteria were published in 2004 and comparisons could be made of trials published before and after this date. Trials published before 1999 were not selected because they are less likely to be subjected to regulatory scrutiny therefore harms reporting may be poorer in this era. Furthermore, these trials would pertain to first generation AEDs where harms data is likely to be very poorly reported. At the time of writing of this thesis additional trials were published but these trials published beyond 2008 were not the scope of this thesis.

A list of inclusion and exclusion criteria is shown below and search protocol is shown in the table below and appendices.

Inclusion Criteria

- Randomised controlled trials- trials where allocation of interventions was randomly assigned to patients.
- Studies published between January 1999 and December 2008 inclusive
- Randomised trials comparing an AED or another AED or placebo
- Patients suffering from epilepsy
- Adults ≥ 18 years old or children <18 years old with epilepsy
- English language
- Commercially funded and non-funded trials
- Outcomes included any seizure related or harms outcome

Exclusion Criteria

- RCTs assessing surgical interventions and/or vagus nerve stimulation
- RCTs of AEDs with neuropsychological outcomes as the primary outcome measure.
- RCTs of AEDs where the primary outcome was a pharmacodynamics or pharmacokinetic measure.
- Observational studies
- Non-human trials
- Non-English studies

6.3.3 Search Methods

Key words in searches used were: "epilepsy", "antiepileptic drugs" and "randomized controlled trials." Limitation functions in search engines automatically excluded trials that were observational studies due to in-built tagging of abstracts. Searches' were limited to trials published between 1999 and 2008. This made search results easier to manage as a large number of trials could be excluded without the need to read abstracts. A search strategy is shown in the appendix G page 317.

6.3.4 Resources used

Searches for trials were made using the following databases:

1. MEDLINE via the PubMed interface,
2. OVID via its home page
3. The Cochrane Registry of Clinical Trials via its online databases of journals.

All studies collected were cross-referenced with the Cochrane library, any duplicates found, were removed.

6.3.5 Selection of studies

To ensure reproducibility of searches, two reviewers searched for RCTs published between January 2003 and December 2003, if the results of searched were comparable then one reviewers searched for the remaining trials. Any disagreements regarding inclusion were resolved after discussion following selection of all trials in the data set. Abstracts were scrutinised for each trial and in some cases the full text of the trial was read.

EpiInfo software was used in epidemiology studies to create an electronic Proforma. This software is available for free download from the CDC website. A paper version of items of data is shown in the appendix. I page 353. *EpiInfo* was used to collect data from clinical trials and this was exported into an excel file. Raw data was stored in an Excel file. Data was inputted into SPSS databases for further analysis.

6.3.6 Data extraction and management

The CONSORT extension for harms outlines ten recommendations for reporting of harms in clinical trials. These pertain to parts of any given trial report for example the title, abstract, introduction and so on. Each CONSORT recommendation therefore would contain many items. All possible items from each of the ten recommendations were extracted by faculty staff and by means of consensus; we included and excluded some items. Therefore, not all items were included. Items for inclusion depended on myself and faculty members or appropriateness for this study (table 25).

Of the ten recommendations, only nine were selected. CONSORT recommendation nine was excluded and not audited Each recommendation has several items and these were extracted from the statements and shown in the table below.

Using the checklist, we screened each RCT for adherence. Two reviewers did this for fourteen trials and Cohen's Kappa statistic was calculated to quantify inter-rater agreement. If inter-rate agreement was deemed acceptable between two reviewers, then one reviewer carried out extraction for the remainder of the trials. To simplify the calculation of κ, we used SPSS version 21 to calculate Cohen's Kappa. We selected fourteen trials for comparison; therefore 322 items in total were compared between two readers. An explanation of Cohen's Kappa is included in the appendix B page 334.

Section of paper	CONSORT Recommendation	Descriptor of CONSORT recommendations for harms	Items Evaluable
Title & Abstract	1	*If the study collected data on harms and benefits, the title or abstract should so state*	1 Adverse events mentioned in title or abstract
Introduction	2	*If the trial addresses both harms and benefits, the introduction should so state*	2 Information on harms mentioned in introduction
Methods	3	*List addresses adverse events with definitions for each (with attention, when relevant to grading expected vs. unexpected events, reference to standardised and validated definitions and descriptions of new definitions)*	3 Definition of AE mentioned 4 If article mentioned all or selected sample of AE 5 If article mentions treatment emergent AE (TEAE) 6 Use of validated instrument to report AE 7 Use of dictionaries for coding of AE
	4	*Clarify how harms related information is collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms related monitoring and stopping rules if pertinent)*	8 Description of how harms data were collected e.g. diaries, phone interviews or face-to-face interviews. 9 Description of when harms data were collected 10 Description of how adverse events were attributed to trial drugs
	5	*Describe any plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures and any statistical analysis)*	11 Description of methods for presenting and analysing harms in methods section. 12 Description of approach for the handling of recurrent events
Results	6	*Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment.*	13 Description of withdrawals due to harms in each arm. 14 Report contains data on serious adverse events and death.
	7	*Provides denominators for describing harms*	16 Provide denominators for harms 17 Provide definitions used for analysis set. 18 If trial states same analysis set used for efficacy and safety.
	8	*Present the absolute risk of each adverse event (specifying type, grade and seriousness per arm) and present appropriate metrics for recurrent events, continuous variables and scale variables whenever pertinent.*	18 Results presented separately for each group 19 Severity and grading of adverse events 20 Provide both number of events and number of patient with events.
	9	*Describe any subgroup analysis and exploratory analysis for harms*	Data not collected as very few trials conduct sub-group analysis
Discussion	10	*Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability and other sources of information on harms*	21 If prior literature is cited in the discussion in relation to adverse events. 22 If the discussion is balanced with regards to efficacy and harms. 23 If limitations of the study are discussed

Table 25 CONSORT recommendations for harms and description of items used- Modified from Ioannidis et al 2004

6.3.7 Assessment of risk of bias in included studies

Each RCT was analysed by one reviewer and the CONSORT score was calculated for each trial. Using the checklist, fourteen studies were analysed and Cohen's Kappa statistical analyses were used to levels of agreement and therefore the risk of selection bias. Selection bias was deemed to be low based on the results of the Kappa statistic. Analysing each trial twice on different occasions further reduced errors in data collection.

Unfortunately, the reviewer was not blinded when extracting data from the trials and this may introduce bias.

6.3.8 Outcome Measures

Two types of data were collected from studies. The first type includes items of data pertaining to the CONSORT score and its calculation. This included a yes and no answers to the 23 items included in the checklist of questions for each trial. It is from this primary data, I conducted the main analysis.

The second type of data from trial reports was supportive data used to further analyse the CONSORT score. Supportive data could be either categorical or numeric. These items included characteristics of individual trials and details of harms reporting in the methods, results and discussion sections. Details of this data are given in section 6.3.12. Data collected was inputted into *EpiInfo*, which severed as an electronic data collection tool, and output of raw data was in the form of Microsoft Access and Microsoft Excel files.

The CONSORT score was calculated from the yes and no answers to 23 items.. Mean CONSORT score was calculated for each trial and for each subgroup within each trial. Subgroups were;

1. Commercially funded vs. Non-commercially funded trials,
2. Trials in adults vs. trials in children versus trial with both adults and children;
3. Studies published before and after the CONSORT statements were published,
4. Trials published in subspecialty journal and general journals.

6.3.9 Other items of data collected

Other items of data were collected as part of the analysis. These items would provide additional data on the reporting of harms. A list of these items is shown in appendix C page 336.

6.3.10 Planned data and statistical analyses

Summary data included the relative risks of trials meeting individual items relating to the CONSORT score and percentage of trials meeting individual items. SPSS and RevMan 5 software were used. Continuous variables were described using arithmetic mean and medians. Frequency distribution of primary and secondary data was displayed using appropriate charts and tables.

Comparisons of CONSORT mean scores of trials published with commercial and non-commercial trials. Pre and post CONSORT studies, trials in adults and children and trials with adults and children. Comparisons were made between trials published in epilepsy and non-epilepsy journal. Additional comparisons were made between trials published in specialty journals and non-speciality journals.

Other analyses performed included; comparison of CONSORT scores between add-on and mono-therapy trials, between multi-centre and single centre studies and between trials that did or did not report a dictionary for harms. I also carried out comparisons between trial using types of seizures, scope of study and number of authors as covariates.

Assuming CONSORT scores followed a normal distribution, unpaired t-test was used to compare means of CONSORT scores between subgroups. Analysis of variance (ANOVA) to compare more than two groups. Equation of the t-test is shown in appendix D page 338.

Student t-test was used to compare the CONSORT scores between subgroups mentioned earlier; therefore, these are independent groups of data.

Pearson's correlation (r) and Scatter plots to illustrate the relationship between continuous variables. Pearson's correlation statistics is explained in appendix E page 339.

Comparisons were made between proportions of items met between subgroups. These proportions were expressed as a percentage of the whole sample size. However, percentages and proportions do not provide confidence intervals where we can assess statistical significance. Thus, one had to convert parentages into relative risks (Morris and Gardner 1988).

Relative risks were chosen over odds ratios as they are not affected by the size of the denominator and they are comparatively easier to understand. Furthermore, relative risks are earlier to transform to logarithmically if needed for future analysis.

Relative risks were quoted with the 95% confidence intervals. When calculating relative risks of individual items, we were not constrained in choosing a fixed or random effects models as summary measures were not to be summated.

6.4 RESULTS

6.4.1 Selection of Clinical trials

Two reviewers searched for trials published in 2007. Two hundred and fifty-seven epilepsy trials were available in that year. Two reviewers assessed for eligibility. One reviewer selected 13 articles and the other reviewer selected the same 13 articles plus one additional article. This was excluded by mutual agreement and one reviewer carried out the remainder of the searches. Therefore, one reviewer could carry out the selection of trials for inclusion.

6.4.2. Results of searches

One hundred and fifty-two trials published between 1999 and 2008 inclusive were selected for analysis. Searches resulted in 2052 citations out of which 1400 were not randomised controlled trials. 76 trials were not in English; 138 trials of other drugs like

galantamine and antidepressant medications were excluded. Excluded also were 146 non-drug interventions and 140 trials with a neuropsychological outcome. The selection of studies in shown in the figure below (fig 34).

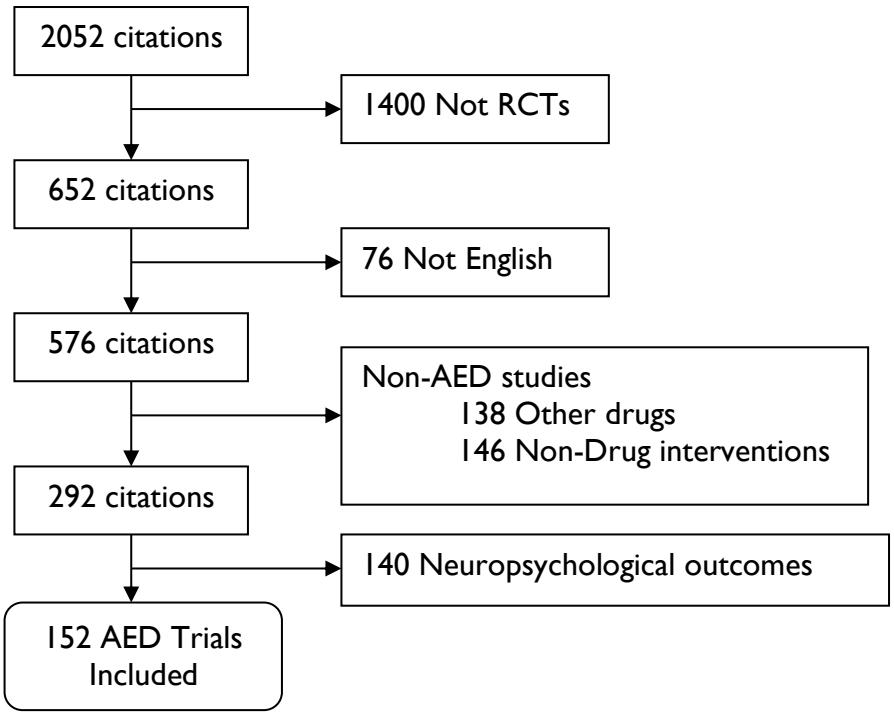


Figure 34 Disposition of clinical trials: Reporting of Harms.

6.4.3 Inter-rater agreement for data extraction

Two reviewers extracted data from trials published in 2007. Overall there was good agreement with the reviewers. The reviewers disagreed in the interpretation of CONSORT recommendation three for reporting of all or selected samples of AEs. After further discussion, all 13 trials were re-assessed by both reviewers and results compared again.

The value of the kappa statistic was 0.78 (95% CI of 0.64 – 0.92) indicating good agreement. The remainder of the trials were analysed by one reviewer. Table 26 shows the results for inter-rater agreement.

Reviewer B x Reviewer A Cross tabulation					
			Reviewer A		Total
			Yes	No	
Reviewer	Yes	Count	231	6	237
		Expected Count	184.7	52.3	237.0
	No	Count	20	65	85
		Expected Count	66.3	18.7	85.0
Total		Count	251	71	322
		Expected Count	251.0	71.0	322.0

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	0.781	.041	14.106	.000
N of Valid Cases		322			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Table 26 Results of inter-rater agreement

6.4.4 Characteristics of studies

One hundred and fifty-two studies were included in this review. Details of included studies are shown in the appendix A page 317. They randomised a total of 30,650 patients with a median number of 135 patients.

The results demonstrate that on a yearly basis approximately 10 to 21 trials in epilepsy were published. There was no pattern on the number of trial published per year (fig 35 page 130).

Of the 152 trials, 94 (61%) were commercially funded and 58 (39%) were non-commercially funded (table 27 page 131). Eighty-six trials (57%) were published before the CONSORT recommendations and 66 (43%) were published after. Eighty-seven trials (57%) were add-on therapy studies and 65 (43%) were mono-therapy studies. Seventy-six were placebo-controlled studies and 76 were not placebo controlled. One hundred and twenty-six trials were multicentre and 26 were single centred. The median duration of trials was 26 weeks the minimum duration was 2 weeks and the maximum was 294 weeks.

Forty nine percent of trials were published in epilepsy journals and 51% in non-epilepsy journals. Fifty eight percent of trials were published in speciality journals and 42% in

non-specialty journals. Thirty-eight articles were published in the journal Neurology and 37 were published in the journal Epilepsia. Seventeen articles were published in the journal Seizure and eleven were published in Epilepsy Research (fig 36 page 131) .

Thirty-five trials reported the dictionary used for harms data, one hundred and seventeen trials did not mention the use of a dictionary.

Some trials quoted the threshold above which adverse events were reported. Forty-six percent of trials mentioned harms thresholds whereas 54% did not report this. Of the trials that reported a threshold, 41 out of 70 trials reported adverse events above a threshold of >10% and 29 out of 70 trials reported adverse events above a threshold of >5%.

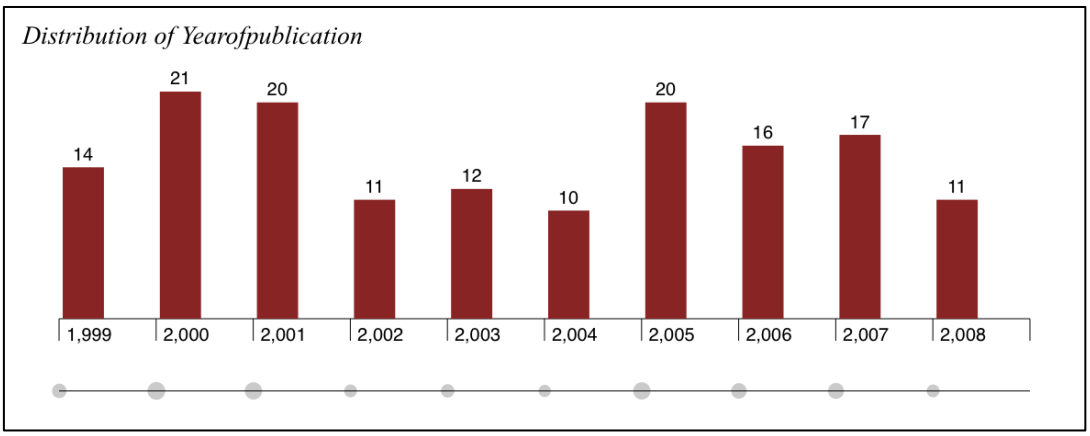


Figure 35 Number of RCTs by year of publication

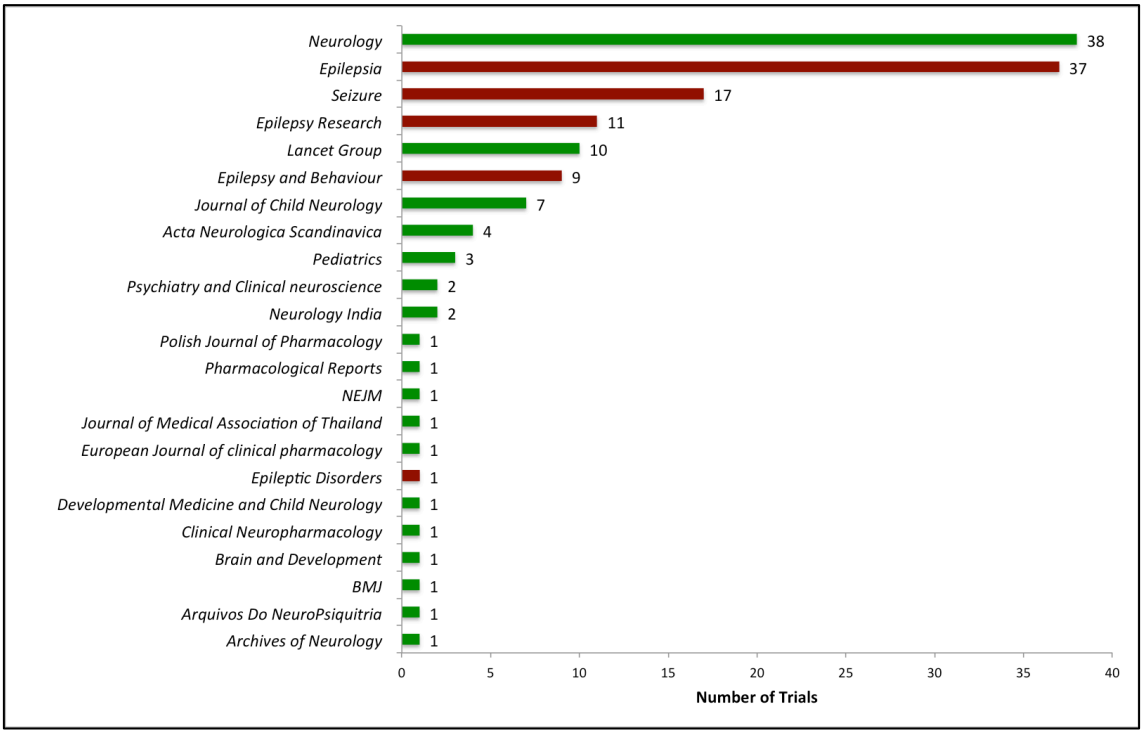


Figure 36 Frequency of trials by journal name: Epilepsy journals are in red and non-epilepsy journals in green

Characteristics of studies		
		Number of trials (%). Total =152
Demographics	Adults Children Both adults and children	79 (52) 35 (23) 38 (25)
Blinding	Double blinded trials Single blinded trials Open label trials	120 (79) 4 (3) 28 (18)
Epilepsy type in population	Focal epilepsy Generalised epilepsy Both focal and generalised epilepsy	102 (67) 8 (5) 42 (28)
Funding	Commercially funded Non-commercially funded	94 (62) 58 (38)
Centre	Multi-centre Single-centre	126 (83) 26 (17)
Comparator	Placebo controlled Actively controlled	75 (49) 77 (51)
Active Intervention	Add-on AED Mono therapy	87 (57) 65 (43)
Journal type	Epilepsy Journal Non-epilepsy Journal	75 (49) 77 (51)
Journal type	Specialty Journal Non-Specialty journal	88 (58) 64 (42)
Dictionary reported	Yes No/not reported	35 (23) 117 (77)
Harms above a certain threshold	Yes No/Not stated	70 (46%) 82 (54%) (41 trials >10%; 29 trials >5%)

Table 27 Characteristics of studies included in analysis

6.4.5 Characteristics of patients

Seventy-nine trials recruited adults, 35 recruited children and 38 recruited adults and children. Seventy-five trials were published in epilepsy journals and 77 in non-epilepsy journals. The median number of patients randomised was 135 and the mean number of patients randomised was 201 patients (fig 37 page 133).

Patients were heterogeneous in the type of epilepsy. Eight trials included patients with generalised epilepsy and 102 trials with focal epilepsy. Forty-two trials had unclassified seizures and were called both focal and generalised.

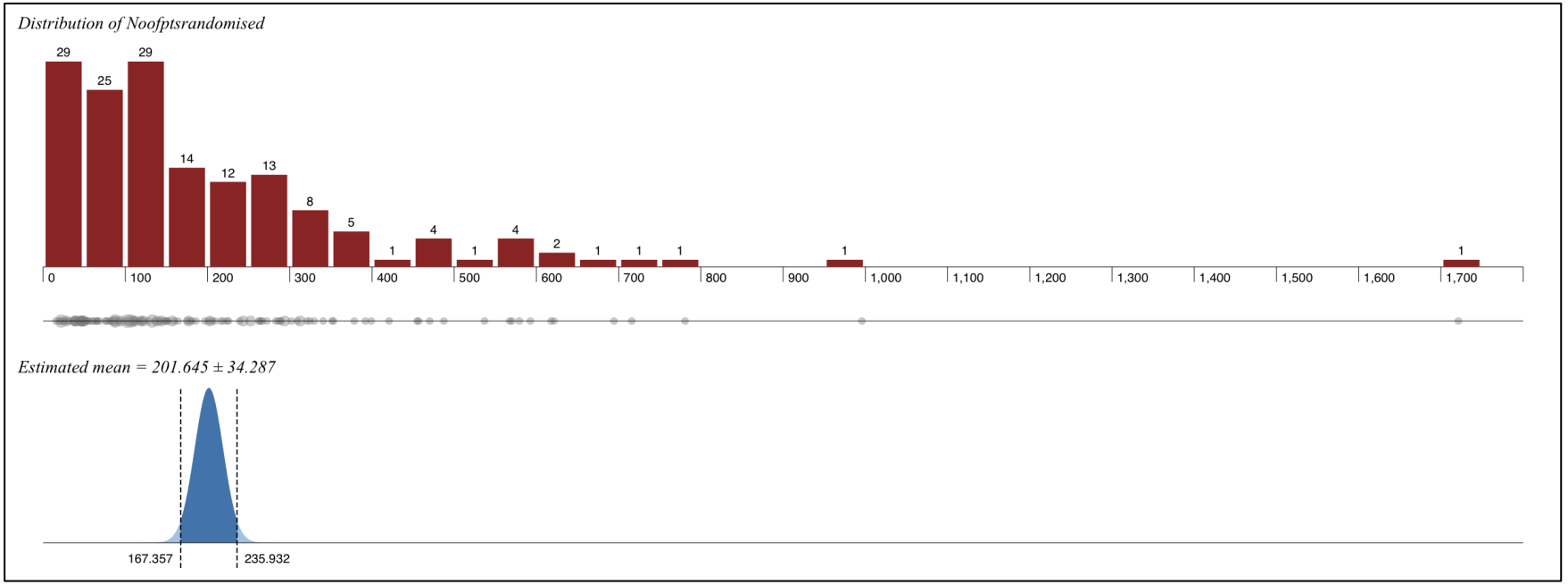


Figure 37 Distribution of number of patients recruited in RCTs of epilepsy

6.4.6 Description of active intervention/interventions

In some of the studies, the active intervention/s or were compared against placebo. Some studies were actively controlled against another AED. Two trials included in the analysis were the SANAD studies, arm A and B. The largest group of trial were trials of topiramate, levetiracetam and lamotrigine (table 28).

Active Intervention	Frequency
Topiramate	21
Levetiracetam	19
Lamotrigine	19
Valproate	12
Vigabatrin	11
Oxcarbazepine	11
Gabapentin	10
Pregabalin	6
Racemaide	6
Tiagabine	5
Midazolam	3

Table 28 Description of active intervention group

6.4.7 Percentage of published document relating to harms data

Using word counts, the total number of words in the results section of the article text and the total number of words used for harms data was calculated. The amount of words was calculated as a percentage. The minimum percent was 0% and the maximum was 70%. The mean percentage was 27% (95% CI of 24.19 to 28.6) (fig 38 page 135). Seven trials did not have any section of the paper for harms results reporting. There is no clear guidance on what constitute the minimum space for reporting of harms data.

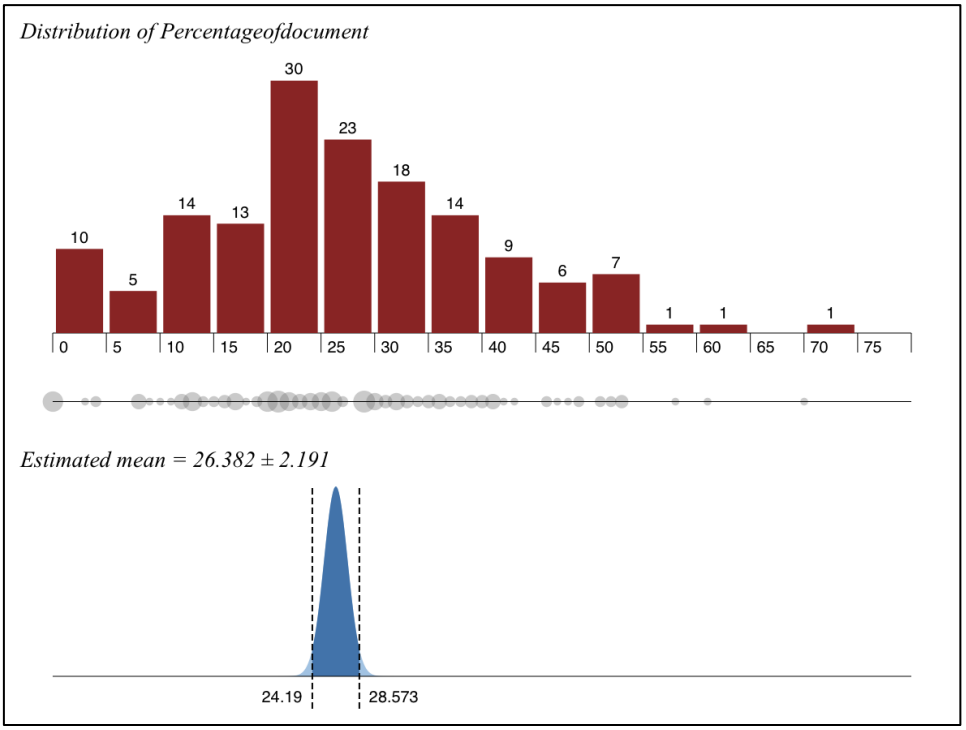


Figure 38 Percentage of the results devoted to harms reporting

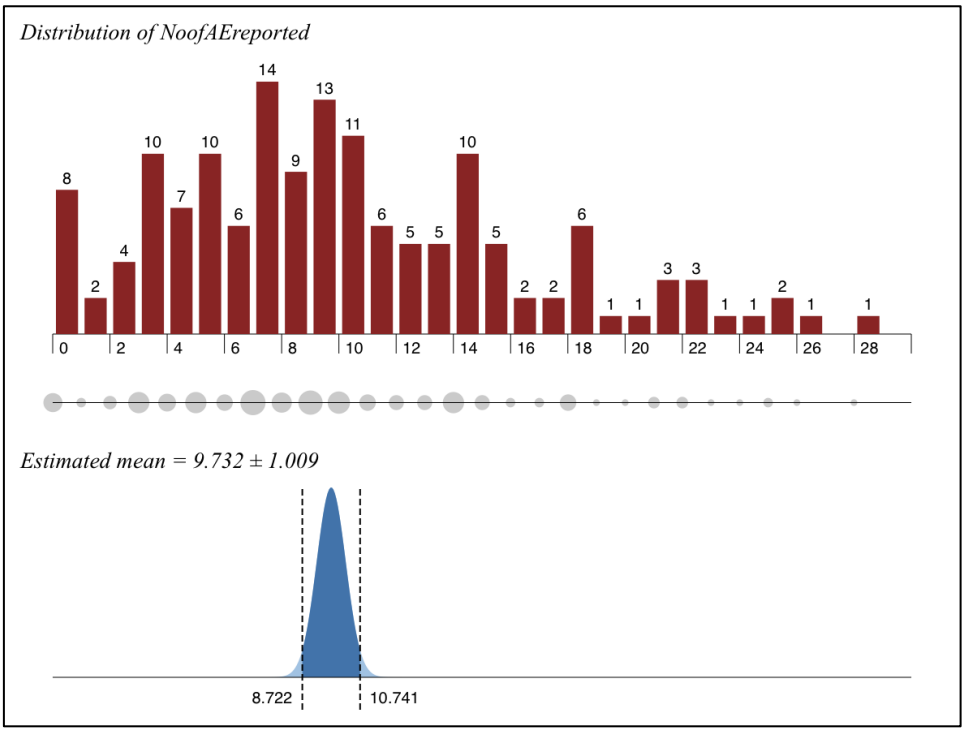


Figure 39 Number of adverse events reported per publication

6.4.8 Number of adverse events reported

Each trial report would cite a table or a list of adverse events. Most trials would report a number of adverse events above a certain threshold of patients reporting these events. Commonly this would be either >5 to 10% of all adverse events obtained from patients. The range of adverse events ranged from 0 to 28. Figure 39 (page 135) shows the frequency distribution of adverse events against number of trial reports. The median number of discrete adverse events reported was nine.

6.4.9 Number of authors per publication

Total number of authors per publication was counted. If the list of authors included a study group, then this was not counted as a single author. Only individuals were counted. If no specific person was mentioned, then the number of authors was counted as missing data. The median number of authors per trial was six.

6.4.10 Distribution of CONSORT scores across all the studies

Twenty-three items from the CONSORT statements were used to create a composite score. The minimum score was 0 and the maximum was 22 (fig 40 page 137). No trial met all 23 items. The mean score was 11.3. A distribution of scores is shown in the graph below. The range of CONSORT scores is from 0 to 22. The median score was 12. The mode is 14. The mean CONSORT score plus one standard deviation gave a score of 16.

A Q-Q plot shows that the distribution of scores is normally distributed without a positive or negative skew (fig 41 page 137). The Shapiro–Wilk test of normality showed a normal distribution rejecting the hypothesis that the distribution is not normally distributed, p value of 0.154. Therefore, this data set would be amenable to further statistical analysis using parametric test such as independent t-test comparing the means of CONSORT scores.

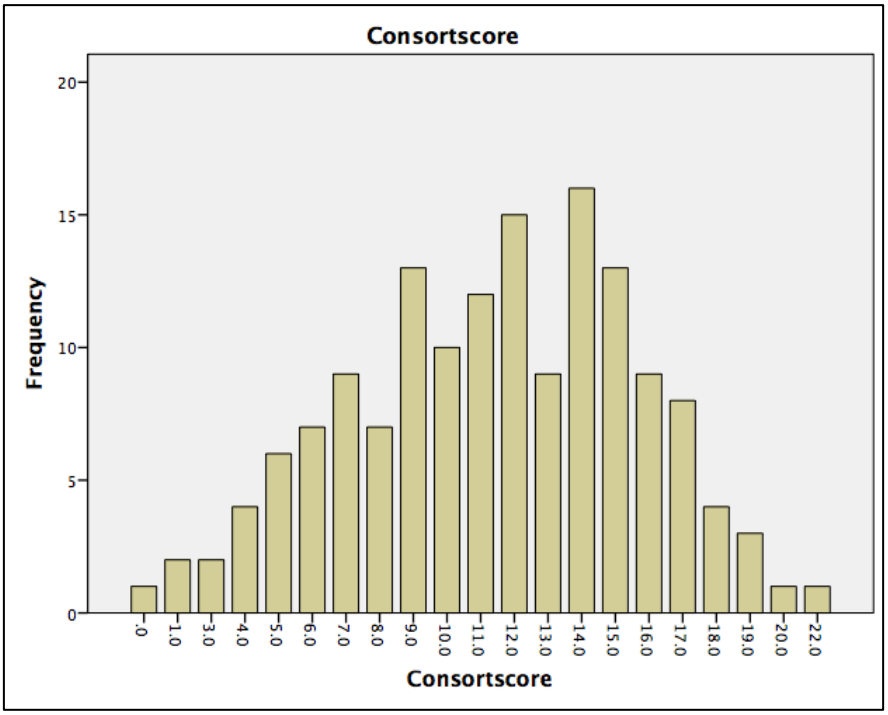


Figure 40 Distribution of CONSORT scores

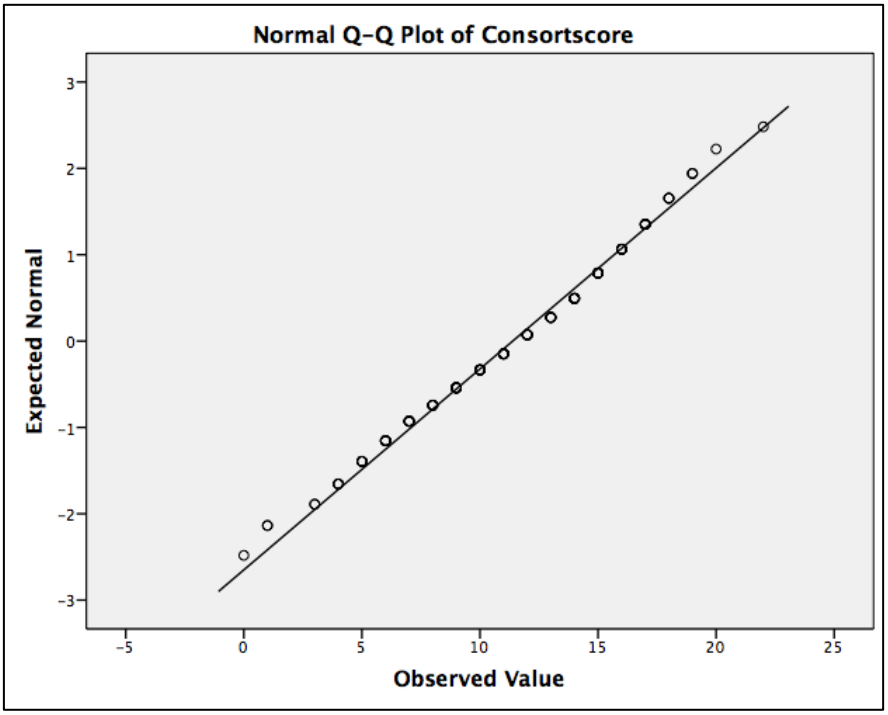
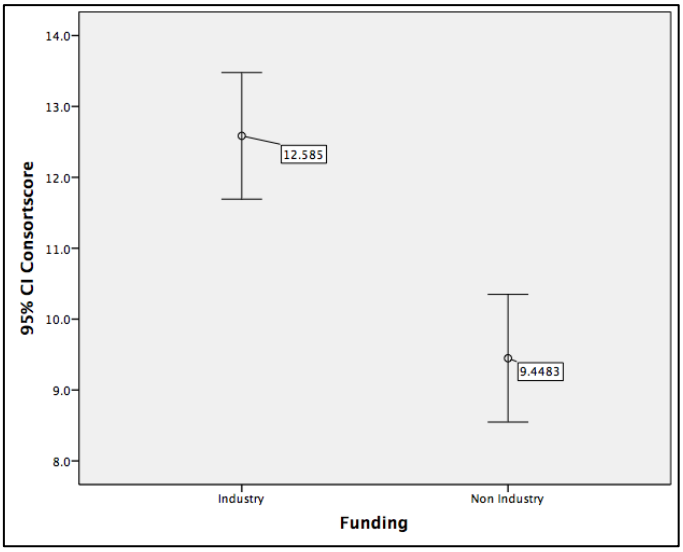


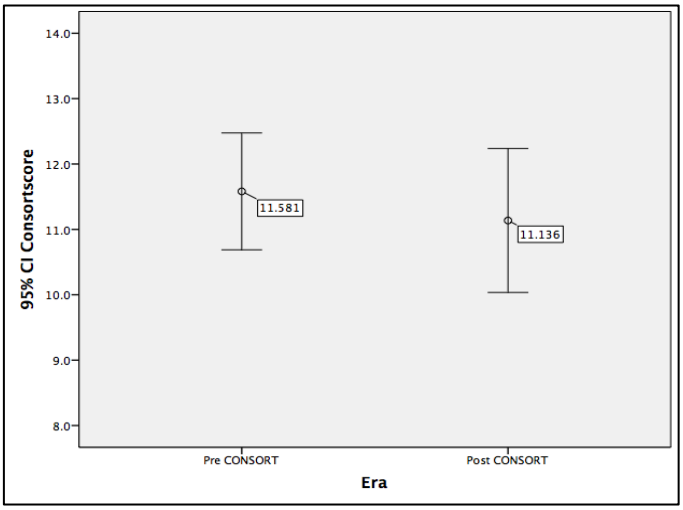
Figure 41 Q-Q plot for normality

The result of CONSORT scores compered between subgroups is shown in table 29 (page 138) and the corresponding error bar plots shown in figure 42 and figure 43 on page 139 to 140.

	Number of trials	Mean CONSORT score	Range of items	Difference of Means	95% confidence intervals for difference of means	P-value
Commercially funded trials	94	12.6	1-21	3.2	1.8 to 4.5	< 0.001
Non-Commercially funded trials	58	9.4	0-17			
Pre-CONSORT trials	86	11.6	0-19	0.5	-0.9 to 1.8	0.529
Post CONSORT trials	66	11.1	3-21			
Adults	79	12.5	3-21	3.2	1.6 to 4.7	<0.001
Children	35	9.3	3-16			
Epilepsy Journals	75	11.4		0	NA	NA
Non- Epilepsy Journals	77	11.4				
Non- Specialty Journal	64	11.5	3-19	0.2	-1.2 to 1.7	0.756
Specialty journal	88	11.3	0-22			
Journals endorsing CONSORT	97	11.1	3-19	-0.8	-0.6 to 2.2	0.279
Journals not endorsing CONSORT	55	11.9	0-22			

Table 29 Mean CONSORT Score and comparison of subgroups





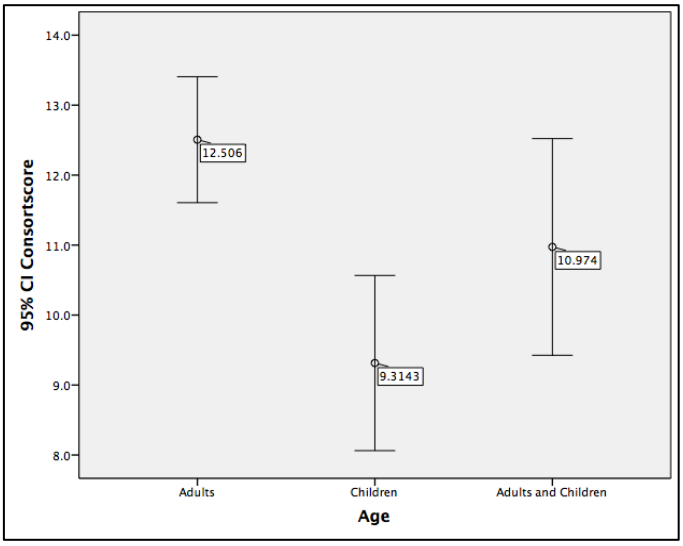
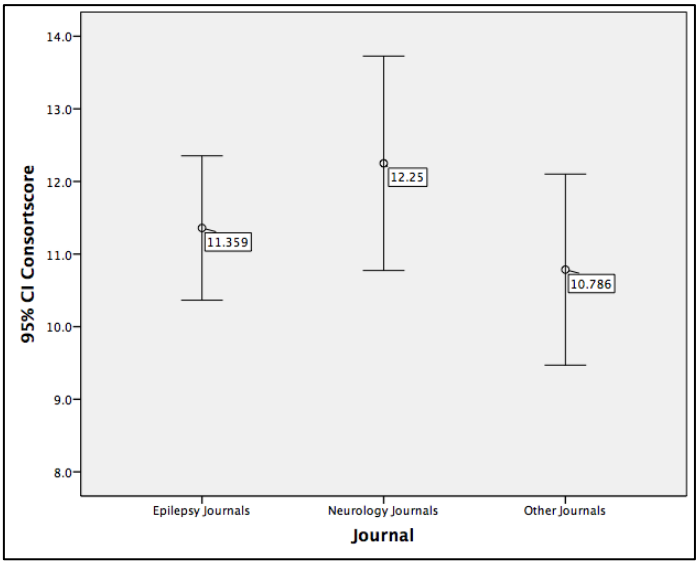
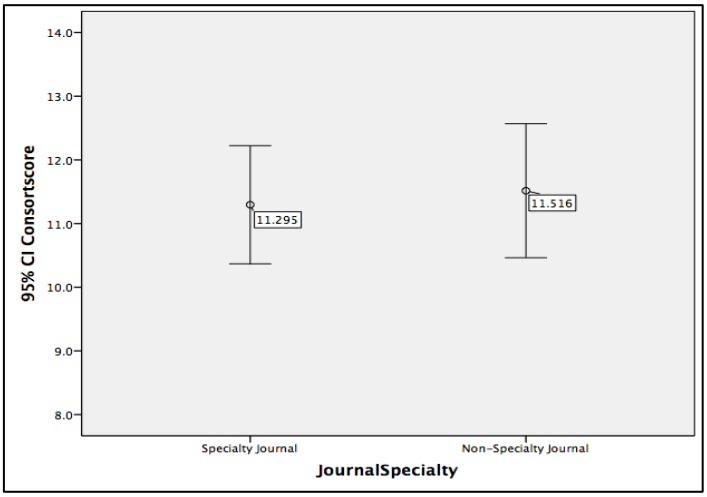


Figure 42 Error bar plots of comparisons of CONSORT scores. Commercial vs. non-commercial; Pre-CONSORT vs. post CONSORT; adult and paediatric studies





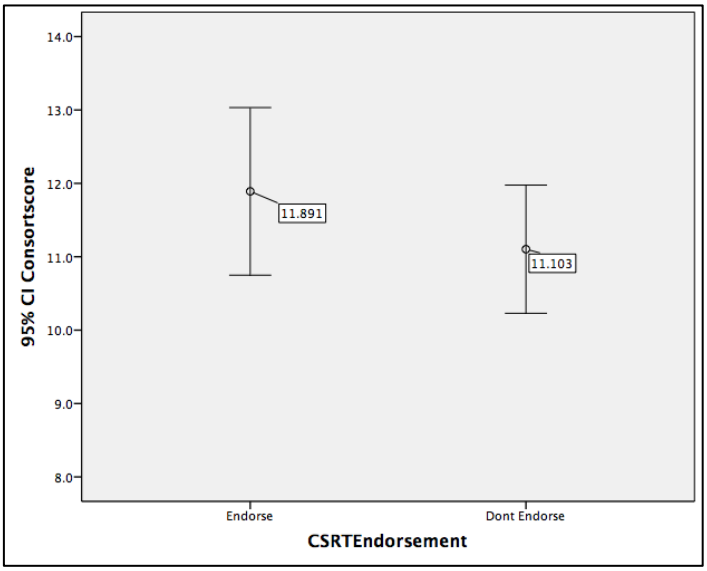


Figure 43 Error bar plots of comparison of CONSORT scores. Journal type; Journal Specialty and journal that do or do not endorse CONSORT

6.4.11 Commercially and non-commercially funded trials

Commercially funded trials reported more items than non-commercially funded trials (mean CONSORT score of 12.6 and 9.4 respectively) with a difference in means of 3.2 (95% confidence interval of 1.8-4.5) this difference was statically significant, $p < 0.001$ See table 29 on page 138 and fig 42 on page 139.

6.4.11.1 Percentage of trials meeting individual items (Commercially and non-commercially funded trials)

For each item, the proportion of trials meeting individual items varied considerably. This ranged from 87.5% for mentioning harms data in title or abstract to 7.2% for handling of recurrent adverse events. Harms in title and abstract were reported best, followed by denominators for adverse events. Other items that were reported well were harms in introduction, timing of adverse events early or late withdrawals, serious adverse events or deaths.

These percentages indicate that meeting of individual items not only is heterogeneous within trials but also between trials there are some items of harms reporting are reported better than others (table 30 page 142).

Harms in introduction and abstracts were described well with percentages of 87.5 and 74.3%. Harms reporting in the methods section corresponding to items 3 to 12 comparably were lower. In this section, the percentages ranged from 15% to 76.3%. Harms reporting in the results section corresponding to items 13 to 20 were also better reported with percentages ranging from 19.1% to 78.3%. Harms reporting in discussion section-items 21, 22 and 23 was also reported well with percentages ranging from 40.8% to 67.8%.

CONSORT item	Item	Percentage of total number of trials meeting item %	CONSORT item	Item	Percentage of total number of trials meeting item %
Harms in title or abstract	1	87.5	Early or late withdrawals	13	71.0
Harms in introduction	2	74.3	Serious AEs or death	14	72.3
Definition of AE	3	36.2	Provide denominators for AEs	15	78.3
All or selected sample	4	31.2	Provide definitions used for analysis set	16	40.1
Treatment emergent AE	5	46.7	Same analysis set used for efficacy and safety	17	34.9
Validated instrument	6	15.8	Results presented separately	18	68.4
Validated dictionary	7	21.7	Severity and grading of AEs	19	47.3
Mode of AE collection	8	56.6	Provide both number of AEs and number of patients with AEs	20	19.1
Timing of AE	9	76.3	Discusses prior AE data	21	67.8
Details of Attribution	10	33.3	Discussion is balanced	22	61.2
Details of presentation and analysis	11	35.5	Discussion of limitations	23	40.8
Handling of recurrent AE	12	7.2			

Table 30 Percentage of Trials meeting individual CONSORT checklist items

6.4.11.2 Relative risks of meeting individual items (Commercially and non-commercially funded trials).

Eleven items were reported more in commercially funded studies than non–commercially funded studies. Details are shown in the table below (table 31 page 144). These eleven items were statistically significant. Relative risks that were significant ranged from 1.01 to 3.46.

Items that were reported better in commercially funded trial were:

1. The definition of adverse events
2. All or a selected sample of adverse events
3. Treatment emergent adverse events
4. Use of the validated dictionary
5. Details of attribution
6. Serious adverse events or death
7. Providing definitions used for analysis set
8. Providing details if the same analysis set used for efficacy or safety
9. Results presented separately
10. The severity and grading of adverse events reported
11. Discussions are balanced

CONSORT Item	Item	Clinical trial section	Relative risk of commercially vs. non-commercially funded trials (95% C.I.)
Harms in title or abstract	1	Introduction	1.09 (0.96-1.25)
Harms in introduction	2	Introduction	0.93 (0.77-1.12)
Definition of AE	**3**	**Methods**	**3.15 (1.67-5.95)**
All or selected sample	**4**	**Methods**	**2.34 (1.27-4.34)**
Treatment emergent AE	**5**	**Methods**	**1.69 (1.12-2.55)**
Validated instrument	6	Methods	1.23 (0.56-2.70)
Validated dictionary	**7**	**Methods**	**3.46 (1.41-8.44)**
Mode of AE collection	8	Methods	1.09 (0.82-1.21)
Timing of AE	9	Methods	1.01 (0.84-1.21)
Details of Attribution	**10**	**Methods**	**1.85 (1.08-3.16)**
Details of presentation and analysis	11	Methods	1.05 (0.67-1.64)
Handling of recurrent AE	12	Methods	2.78 (0.62-12.40)
Early or late withdrawals	13	Results	1.09 (0.88-1.36)
Serious AEs or death	**14**	**Results**	**1.27 (1.01-1.59)**
Provide denominators for AEs	15	Results	1.17 (0.97-1.42)
Provide definitions used for analysis set	**16**	**Results**	**2.07 (1.26-3.41)**
Same analysis set used for efficacy and safety	**17**	**Results**	**2.04 (1.09-3.81)**
Results presented separately	**18**	**Results**	**1.45 (1.12-1.89)**
Severity and grading of AEs	**19**	**Results**	**1.50 (1.02- 2.21)**
Provide both number of AEs and number of patients with AEs	20	Results	1.62 (0.77- 3.41)
Discusses prior AE data	21	Discussion	1.25 (0.98-1.60)
Discussion is balanced	**22**	**Discussion**	**1.51 (1.11-2.05)**
Discussion of limitations	23	Discussion	1.20 (0.80-1.82)

Table 31 Relative risk of Meeting individual items, commercial and non-commercial studies: Significant items are in bold.

6.4.12 Pre-CONSORT and Post-CONSORT studies

Pre and post-CONSORT scores were compared and I found no statistical difference in the mean scores between groups. The Mean score was 11.6 in the Pre-CONSORT groups and 11.1 in the post-CONSORT group. The difference of means was 0.5 and this was found to be not statistically different (CI of the difference in means was -0.9 to 1.8) (table 29 and fig 42 page 138-9).

6.4.12.1 Sensitivity analysis: Pre-CONSORT and Post-CONSORT

As trial may take time to adopt the CONSORT statements, we carried out a second analysis where post-CONSORT we defined as trials published after December 2006. This analysis showed no significant differences between pre-and post CONSORT scores. There were 124 pre-CONSORT studies and 28 post-CONSORT studies. The mean score pre-CONSORT was 11.6 and the post CONSORT score was 12.4. The difference of means was 1.2 with a 95% CI for difference of means of -3.0 to 0.5. Therefore, this difference was not statistically significant.

6.4.12.2 Relative risks of meeting individual items (Pre-CONSORT and Post-CONOSRT trials).

When comparing the relative risks of pre and post CONSORT studies, only one out of 23 items was statistically significant with a validated dictionary reported better in pre CONSORT studies (RR 0.35 CI 0.16- 0.76). The other items the relative risk estimates was greater than one in some and less than one in some items but these included unity in the 95% confidence intervals therefore the difference in relative risks was not statistically significant (table 32 page 146).

CONSORT Item	Item	Clinical trial section	Relative risk of Pre-CONSORT vs. Post CONSORT studies (95% C.I.)
Harms in title or abstract	1	Introduction	1.01 (0.89-1.13)
Harms in introduction	2	Introduction	1.11 (0.92-1.34)
Definition of AE	3	Methods	0.63 (0.69-1.76)
All or selected sample	4	Methods	1.10 (0.69-1.76)
Treatment emergent AE	5	Methods	1.34 (0.96-1.88)
Validated instrument	6	Methods	1.10 (0.53-2.30)
Validated dictionary	**7**	**Methods**	**0.35 (0.16-0.76)**
Mode of AE collection	8	Methods	0.94 (0.71-1.25)
Timing of AE	9	Methods	0.95 (0.79-1.14)
Details of Attribution	10	Methods	1.30 (0.84-2.02)
Details of presentation and analysis	11	Methods	0.83 (0.53-1.29)
Handling of recurrent AE	12	Methods	0.29 (0.06-1.30)
Early or late withdrawals	13	Results	1.80 (0.64-1.30)
Serious AEs or death	14	Results	1.11 (0.97-1.28)
Provide denominators for AEs	15	Results	0.96 (0.80-1.59)
Provide definitions used for analysis set	16	Results	0.90 (0.61-1.35)
Same analysis set used for efficacy and safety	17	Results	0.94 (0.56-1.57)
Results presented separately	18	Results	0.99 (0.80-1.24)
Severity and grading of AEs	19	Results	0.83 (0.59- 1.18)
Provide both number of AEs and number of patients with AEs	20	Results	1.22 (0.63- 2.34)
Discusses prior AE data	21	Discussion	1.14 (0.92-1.41)
Discussion is balanced	22	Discussion	1.07 (0.83-1.38)
Discussion of limitations	23	Discussion	0.94 (0.64-1.39)

Table 32 Relative risk of meeting individual items pre and post CONSORT: Significant items are in bold

6.4.13 **Adults versus Children**

Seventy-nine trials recruiting adults and 35 trials recruiting children were found. Thirty-eight trials recruited both adults' and children and these trials were excluded from the analysis. Mean CONSORT score of trials recruiting adults was 12.5 and the mean score of trials recurring children was 9.3 (table 29 and fig 42). The difference in means was 3.2 with a 95% confidence interval of 1.6 to 4.7. This result was statistically significant at a p value of <0.001.

When comparing which items were reported better in adult trials, we found that four items were reported better in adult trials: Definition of adverse events; details of presentation and analysis; early and late withdrawals and results presented separately. The relative risks for these items did not include unity in the confidence intervals (table 33 page 148).

CONSORT Item	Item	Clinical trial section	Relative risk of Adults trials vs. trials of children (95% C.I.)
Harms in title or abstract	1	Introduction	1.09 (0.91-1.31)
Harms in introduction	2	Introduction	1.13 (0.88-1.45)
Definition of AE	**3**	**Methods**	**2.32 (1.07-5.02)**
All or selected sample	4	Methods	1.44 (0.73-2.84)
Treatment emergent AE	5	Methods	1.33 (0.79-2.21)
Validated instrument	6	Methods	1.39 (0.49-3.49)
Validated dictionary	7	Methods	1.67 (0.68-4.08)
Mode of AE collection	8	Methods	1.32 (0.88-1.96)
Timing of AE	9	Methods	1.18 (0.90-1.53)
Details of Attribution	10	Methods	1.27 (0.70-2.30)
Details of presentation and analysis	**11**	**Methods**	**2.05 (1.01-4.15)**
Handling of recurrent AE	12	Methods	1.59 (0.36-7.12)
Early or late withdrawals	**13**	**Results**	**1.66 (1.16-2.37)**
Serious AEs or death	14	Results	0.99 (0.79-1.25)
Provide denominators for AEs	15	Results	1.23 (0.95-1.59)
Provide definitions used for analysis set	16	Results	1.77 (0.96-3.25)
Same analysis set used for efficacy and safety	17	Results	1.53 (0.74-3.19)
Results presented separately	**18**	**Results**	**1.80 (1.21-2.69)**
Severity and grading of AEs	19	Results	0.88 (0.60-1.31)
Provide both number of AEs and number of patients with AEs	20	Results	2.09 (0.77-5.65)
Discusses prior AE data	21	Discussion	0.91 (0.70-1.18)
Discussion is balanced	22	Discussion	1.13 (0.82-1.57)
Discussion of limitations	23	Discussion	1.10 (0.67-1.81)

Table 33 Relative risk of meeting individual items, adults vs. children: Significant items are in bold

6.4.14 Epilepsy Journals versus non- Epilepsy Journals

One might expect that trials reported in subspecialty journals would be better than general journals such as JAMA or Neurology. Overall trials published in epilepsy journal scored 11.4 and trials published in non-epilepsy journals scores 11.4 with a difference of means of zero (table 29 fig 43). Therefore, there were no overall differences. When individual items were compared, no item showed a significant difference because the confidence interval included unity, see table 34 page 150.

CONSORT Item	Item	Clinical trial section	Relative risk of Epilepsy vs. Non-Epilepsy Journals (95% C.I.)
Harms in title or abstract	1	Introduction	1.04 (0.94-1.16)
Harms in introduction	2	Introduction	1.04 (0.87-1.26)
Definition of AE	3	Methods	1.15 (0.70-1.78)
All or selected sample	4	Methods	1.12 (0.80-1.57)
Treatment emergent AE	5	Methods	1.12 (0.80-1.57)
Validated instrument	6	Methods	1.21 (0.58-2.54)
Validated dictionary	7	Methods	1.23 (0.67-2.26)
Mode of AE collection	8	Methods	0.98 (0.74-1.29)
Timing of AE	9	Methods	0.99 (0.83-1.18)
Details of Attribution	10	Methods	0.88 (0.57-1.37)
Details of presentation and analysis	11	Methods	0.71 (0.45-1.10)
Handling of recurrent AE	12	Methods	1.23 (0.39-3.87)
Early or late withdrawals	**13**	**Results**	**0.79 (0.64-0.97)**
Serious AEs or death	14	Results	0.99 (0.81-1.21)
Provide denominators for AEs	15	Results	1.01 (0.85-1.19)
Provide definitions used for analysis set	16	Results	0.99 (0.67-1.47)
Same analysis set used for efficacy and safety	17	Results	0.98 (0.59-1.63)
Results presented separately	18	Results	1.11 (0.89-1.38)
Severity and grading of AEs	19	Results	0.73 (0.52-1.03)
Provide both number of AEs and number of patients with AEs	20	Results	0.63 (0.32-1.24)
Discusses prior AE data	21	Discussion	1.23 (0.39-3.87)
Discussion is balanced	22	Discussion	0.79 (0.64-0.97)
Discussion of limitations	23	Discussion	0.99 (0.81-1.21)

Table 34 Relative Risk of meeting individual item, epilepsy vs. non-epilepsy journals: significant items are shown in bold.

6.4.15 **Specialty and Non-Specialty Journals**

Comparisons of trials published in specialty and non-specialty journals were made. I found that in terms of reporting, there was no overall difference in CONSORT scores. We expected the specialty journal to score lower than non-specialty journal due to the fact that specialty journals are less likely to endorse the CONSORT statements. Specialty journals scored 11.3, compared to specialty journals, which scored 11.5. The difference in means was -0.2 with a 95% CI of -1.2 to 1.7 (table 29 fig 43).

As stated earlier the 67% of the trials were published in four leading journals. These include in order of frequency: *Neurology* followed by *Epilepsia, Seizure* and *Epilepsy Research*. Only *Neurology* has endorsed the CONSORT statements.

Comparisons were made between journals that do and do not endorse CONSORT. RCTs in journals endorsing CONSORT scored 11.1 versus 11.9 in journal that do not endorse CONSORT. Therefore, the difference in means was not significant between these two groups.

6.4.16 Which items matter in the subgroups?

Items that were reported well and reached statistical significance are shown in table 35 page 152. Thirteen items were reported well in commercially funded trials versus non-commercial funded trials. Only validated dictionary was reported well in pre-CONSORT studies. Four items were reported well in adult trials and one item was reported well in Epilepsy journals.

	Commercial vs. non-commercial	Post CONSORT vs. Pre CONSORT	Adults vs. children	Epilepsy Vs. Non-epilepsy journals
Items reported well and reached statistical significance	Definitions of AE All or selected sample Treatment emergent AE Validated Dictionary Details of attribution Serious AE or death Provide definitions used for analysis set Same analysis set used for efficacy and safety Results presented separately Severity and grading of AE Discussion is balanced	Validated dictionary	Definition of AE Details of presentation and analysis Early of late withdrawals Results presented separately	Early or late withdrawals
Direction of effect	Items favours Commercially funded studies	Item favoured Pre-CONSORT studies	Items favoured trials recruiting adults	Favoured non-epilepsy journal

Table 35 Items that were statistically significant between groups

6.4.17 Other Comparisons made

Covariates	Number of trials per group	Mean CONSORT Scores	Difference in means	P value (t test or ANOVA)
Add-on vs. Mono-therapy	87 65	11.8 10.8	1	0.18
Multi-centre Single centre	126 26	11.8 9.4	2.4	0.007
Dictionary mentioned Yes No/not stated	 117 35	 13.9 10.7	3.2	<0.001
Epilepsy type Focal Generalized Focal and Generalized Other	 89 40 15 8	 12.2 11.6 10.4 9.2 10	 3 2.4 1.2 0 0.8	0.032
Scope of trial Efficacy and Safety Efficacy only Safety only Not stated	 126 13 10 3	 14.3 10.8 10.7 8.5 9	 5.8 2.3 2.2 0 0.5	<0.001

Table 36 Other comparisons made

A comparison of add-on vs. Mono-therapy trials did not reveal any difference in means of scores. Trials that were multicentre scores better than single-centre studies. Trial with focal epilepsy scored higher that trials with other epilepsies and trials where the outcome was efficacy and safety scored better than trials with safety only (table 36).

6.4.18 CONSORT score and interventions

When CONSORT score is plotted against interventions one trial of retigabine had the highest CONSORT score and the lowest score was one trial of Phenytoin. (fig 44).

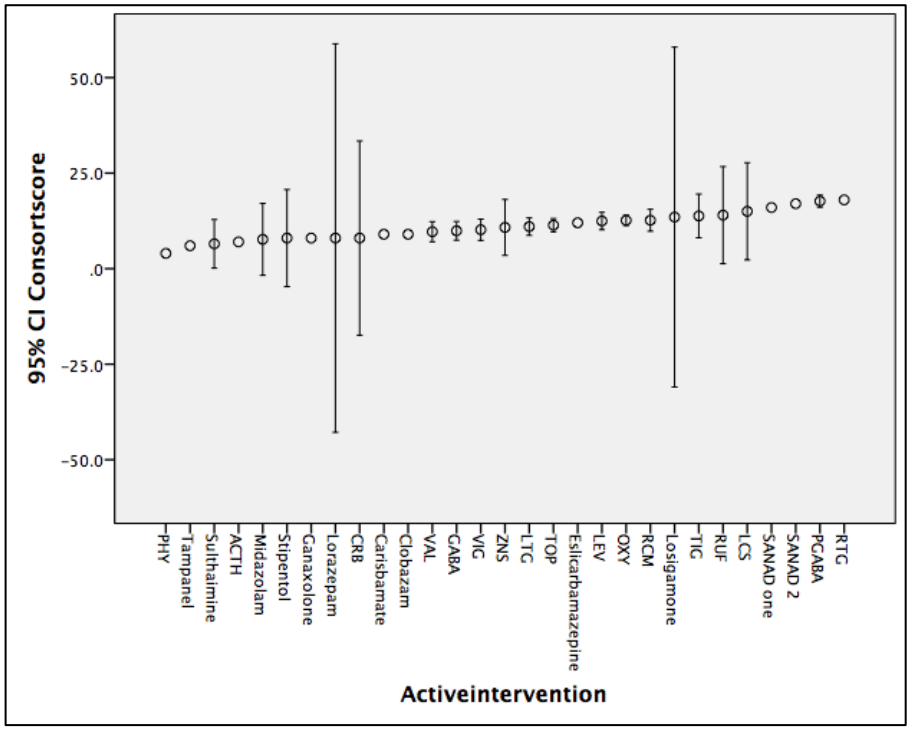


Figure 44 CONSORT Score versus intervention (see abbreviation list on page x)

6.4.19 Study predictors of CONSORT scores

This section discusses the relationship between the CONSORT score and other continuous variables. Comparisons were made between CONSORT score and number of patients randomized, number of adverse events reported and CONSORT Score.

6.4.19.1 Correlation between CONSORT score and number of patients randomised

Pearson's correlation was carried out between the numbers of patients randomized to each trial. Three trials were very large trials that could be considered outliers for this analysis. Therefore, the two SANAD and MESS studies were excluded from this analysis and one other study that randomized approximately a thousand patients was also excluded (Marson et al 2006). A Pearson's correlation of 0.3 was obtained. This means that the correlation between the number of patients randomized and CONSORT score was medium. If the three excluded trials were used the Pearson's correlation showed an R-value of 0.286 (fig 45).

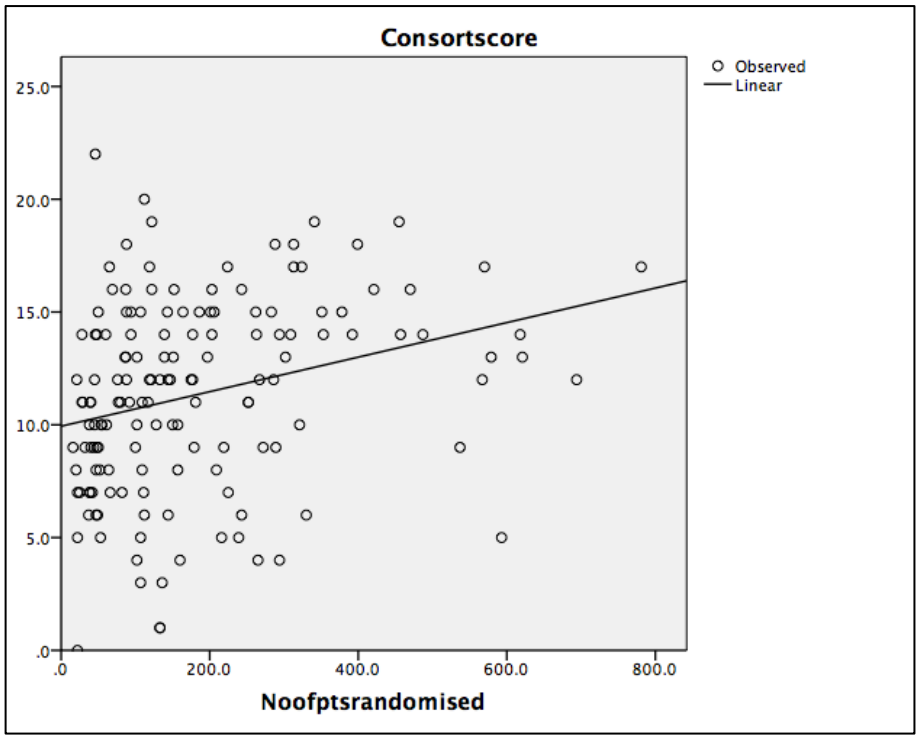


Figure 45 Correlation between CONSORT Score and number of patients randomized

6.4.19.2 Correlation between CONSORT score and percentage of document used for harms data

A correlation between CONSORT score and percentage of document used to report harms was a positive one. The scatter plot below shows a possible positive correlation. A Pearson's correlation showed as positive relationship with a Pearson's correlation of 0.42 (fig 46).

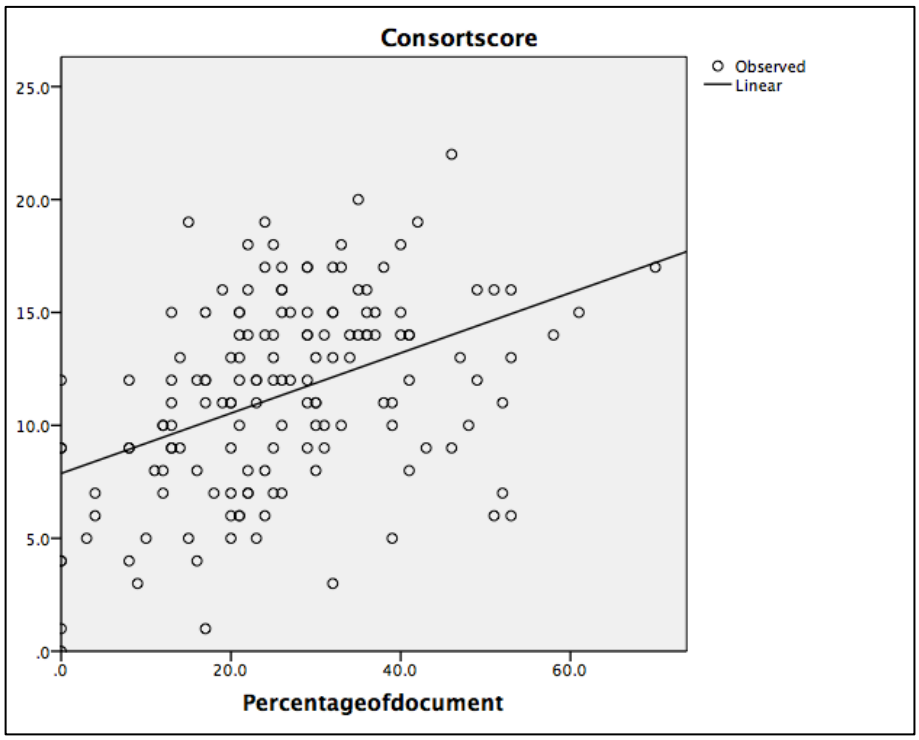


Figure 46 Correlation between CONSORT score and percentage of trial document space used to report harms data

6.4.19.3 Correlation between the CONSORT score and the number of AE reported.

One might expect a linear correlation between the quality of reporting and the number of adverse events reported. This analysis showed a positive correlation but the strength of the correlation was weak; Pearson's R = 0.2 (fig 47).

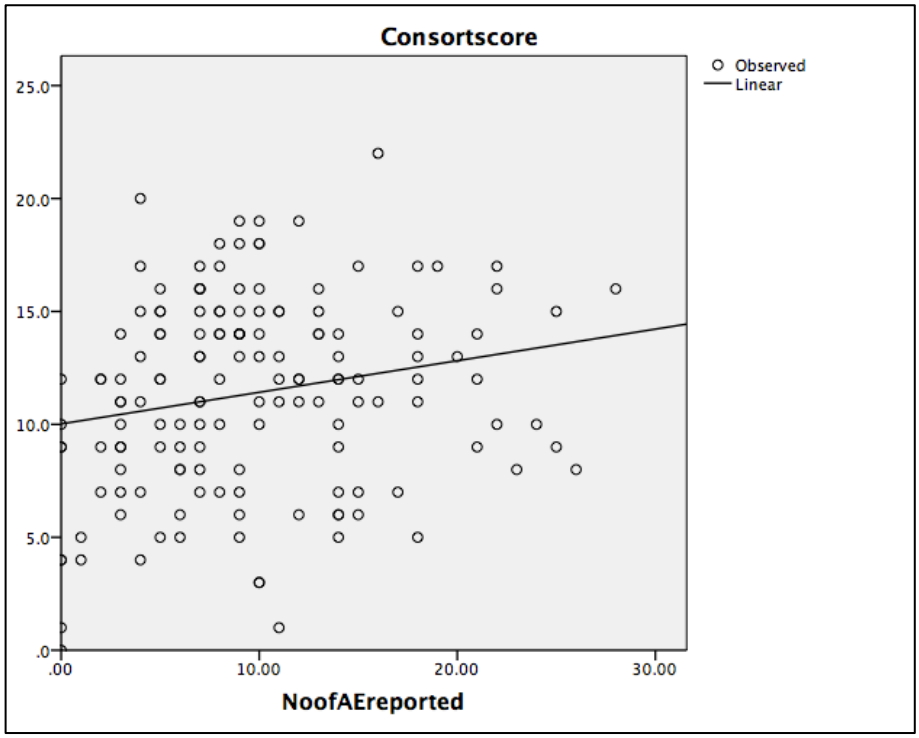


Figure 47 Correlation between the CONSORT score and the number of AE categories reported

6.4.20 Other data items

Only eight trials reported evidence of priming of harms during collection of harms data (table 37). Only ten trials reported if the person attributing harms to intervention or comparator was blinded to the allocated treatment. Eighty-one percent of trials expressed harms data with mean median or percentages. Twenty-eight trials reported the cumulative incidence of adverse events. Only 37.5 percent of trials reported if deaths occurred or not. Only two trials gave additional data of harms on a webpage or in appendices. A tabular description of adverse events was reported in 114 (75%) of trials.

CONSORT Recommendation	Descriptive	Results Number of trials (%) N = 152
3	Evidence of priming	8 (5.3)
4	Was attribution blinded to the assigned treatment?	10 (6.6)
5	Mean medians and descriptive data of harms reported	123 (81.0)
6	Kaplan Meir cumulative incidence of AE	31 (20.3)
6	Authors always report deaths	57 (37.5)
8	Present graphical representation of the number of events per patient or time to event	31 (20.3)
10	Additional harms data in webpage	2 (1.3)

Table 37 Additional items analysed

6.5 DISCUSSION

Epilepsy is a chronic condition where treatment is expected to be life-long. Information on possible harms of AEDs is useful when discussing this with patients. Common questions patients ask is whether to start treatment and what the best treatments are. The MESS and SANAD studies provide the best answers to some of these questions (Marson et al 2007) (Kurmholtz et al 2015).

Randomised controlled trials provide information of harms on short-term harms. Harms are important in making informed treatment decisions; however, reporting of harms in trials may be insufficient.

This study examined the reporting of adverse events in trials of antiepileptic drugs. Presented here are the findings:

6.5.1 Epilepsy trials

One hundred and fifty-two trials were selected for inclusion. In the interests of time, trials beyond 2008 were not analysed. The top four journals were: *Neurology* – a general neurology journal and in three subspecialty journals- *Epilepsia, Epilepsy Research* and *Seizure*. It is expected that journal editors have a considerable influence of the content of RCT reporting. The International Committee of Medical Journal Editors endorses the CONSORT statements. At the time of writing *Epilepsia* and *Epilepsy Research* do not endorse CONSORT statements. This study demonstrated if journal type could be a covariate and we found that there was no significant difference by journal type or if it was a specialty or a general journal. This is not in keeping with data from other studies, which showed that journals that endorse CONSORT are better, compared with non-endorsers (Kane et al 2007) (Kiehna et al 2011).

These RCTs ranged from small to large studies. The most common intervention was topiramate followed by levetiracetam and lamotrigine. The data-set included in this study was therefore a mixed population of specialty and non-specialty journals. The most common trial was topiramate and this reflects the time period chosen for inclusion of trials. Many trials of older AEDs like valproate, phenytoin and

carbamazepine were published before 1999. Trials published before 1999 were not included, as these trials are very likely to be poorly reported.

6.5.2 Quality of harms reporting

A composite score was created from items suggested in the CONSORT recommendations for harms. Unlike the original CONSORT statements, the extension for harms did not include a checklist as an appendix. Therefore, we had to create our own checklist as displayed in this chapter. Other studies have also created a composite score from items in the CONSORT recommendations (Siverndran et al 2014, Cornelius et al 2013, Faggion et al 2013, Breau et al 2010 and Bagul & Kirkham 2011). This checklist is by no means a fully comprehensive checklist. Therefore, checklists are not uniform across studies and although there were similarities, there were also many differences. It would be useful if the authors of the CONSORT statements for harms provided a standard checklist. This would make comparisons across studies more meaningful.

This study is the first on harm reporting in epilepsy. The methods used here were similar to methods used by others in creating a composite score. This study considered 23 items from the CONSORT statements for harms and no trial reported all 23 items. Mean CONSORT score was 11.3. A score of 16 includes the mean plus one standard deviation. The proportion of trials in the dataset that scored greater or equal to 16.0 was 17%. It would therefore not be unreasonable to suggest that the remaining 83% of trials are deficient in their reporting.

The mean number of items reported across all trials was eleven. The median score was twelve. Distribution of the CONSORT score followed a Gaussian distribution therefore statistical assumptions for t-tests and ANOVA were met. Sivendran et al found a similar spread of CONSORT score for harms, but they included only 14 items in their analysis (Sivendran et al 2014). It is evident that reporting of harms is heterogeneous and other authors noted this with similar work in this area (Smith et al 2008).

One trial of retigabine scored the best followed by the SANAD studies. The study that scored the least was a phenytoin trial. One hypothesizes that phenytoin study scored poorly as harms may not have been a primary outcome of the study. Only two trials mentioned the CONSORT statements explicitly in the text of the report. However, none of the trials analysed mentioned the CONSORT extension statements for harms explicitly.

6.5.3 Commercially funded trials

Comparisons of subgroups of studies revealed that there was a consistent trend of better harms reporting in commercially funded studies versus non-commercially funded studies. Specific items were best reported in commercially funded studies. Commercially funded trials were better in reporting all 23 items when compared to non-commercial studies however only eleven of these items were statistically significant. Although this may seem obvious that commercially funded would diminish harms data in trial reports to improve the chance of obtaining a commercial license, but we see that the opposite is true. One can explain this by saying that commercially funded trials would report harms better as they would aim for significant disclosure to facilitate the granting of a license. Also, commercially funded trials will have the necessary resources to collect and therefore present harms.

Of the eleven items that were better reported were serious adverse events and providing adverse events separately. These items are important when trials are used in systematic reviews and the implication is that non-commercial studies would therefore be less likely to be meta-analysed if the outcomes are not reported properly. Commercially funded trials report a dictionary more than non-commercially funded studies. This is expected as regulatory authorities expect that clinical trials have used the preferred terms for adverse events. MEDRA and WHOART are examples of dictionaries that are approved by the EMA and MRHA in the UK for drug licensing.

Similar work done by Faggion et al compared 10 items from the CONSORT statements for harms in two hundred and forty-six trials. They compared commercial and non-commercially funded periodontology trials and they found that the quality of the studies did not differ between the two groups (Faggion et al 2013).

Breau et al compared industry and non-industry trials of harms reported in the urological literature and found that there was a significant difference between the two groups but they did not comment on the magnitude of difference and they did not elaborate on which items were better reported (Breau et al 2010).

Jones et al explored the reasons for why commercially funded trials are better in another study. Their hypothesis was that commercial funded trials would be of a lower quality than non-commercially funded studies. However, their study showed that commercial trials were better. They concluded that commercially funded trials are larger and therefore would be more likely to avoid key biases required for Cochrane reviews (Jones et al 2010). They explain this because commercial trials have an incentive to increase the quality of their work.

One might expect that commercial funded trials might report harms poorly. A recent study by Nieto et al showed that adverse drug reactions in commercial trials were less frequent than non-commercial studies (34.5% vs. 65.1%) (Nieto et al 2007). Reasons cited for this include financial conflict of interest with regard to authors of studies. Trials published by commercial sponsors were not different in methodological aspects but differed in the results. Commercially funded trials were superior to non-funded trials with respect to methodology but are more likely to have a placebo as a comparator therefore are more likely to yield positive results than non-commercial studies. (Schott et al 2010).

6.5.4 Has reporting improved after the 2004 extension statements?

This study demonstrated that there has been there has no improvement or change in reporting of adverse events pre and post CONSORT publication. The mean score pre CONSORT was 11.6 and 11.1 post CONSORT. When comparing individual items pre and post CONSORT we found that all expect one item (use of a validated dictionary) had relative risk including unity therefore were not statistically significant. The use of a validated dictionary was reported better in pre CONSORT studies. Reasons for why this is unclear.

Cornelius et al compared the reporting of harms before and after the publication of the CONSORT guidelines (2013). Their study compared the quality of reporting before and after 2004 but they did not comment if the quality of reporting had improved pre or post CONSORT. A study by Faggion evaluated trials published in 2001-2003 with trials published between 2011 and 2012 inclusive (Faggion 2013). They found that there were no differences in reporting of harms pre and post CONSORT. Anttila et al compared the 1996 CONSORT statements and found no change before and after reporting of trial reporting in paediatric journals (2006). They cite the reason being that paediatric studies are reported in specialty journals and not general journals therefore the quality of reporting is poorer (Anttila et al 2006).

Some evidence that the CONSORT statements have helped with the reporting of trials comes from a paper by Altman et al (2005). They evaluated only CONSORT endorsing journals. One hundred and sixty-seven journals were evaluated. Only 22% of journals mentioned the CONSORT statements in instruction to authors, this was worse in specialty journals (18%) compared with general journals (22%). Forty three percent of journals mentioned the ICMJE website but they didn't mention the ICJME guidelines. (Altman et al 2005).

A sensitivity analysis was conducted to see if changing post CONOSRT studies to include studies published in 2006 and beyond had any difference to the CONSORT score. With this amended benchmark, no difference was found between pre and post CONSORT reporting. However, this may be due to lack of precision and we may need more trials. Nevertheless, when one compared our findings to other studies, they too found no change in reporting post-CONSORT.

There was no difference in CONSORT scores between CONSORT endorsers and non-endorsers. A study by Plint et al only looked at journal that do endorse consort and they concluded that the guidelines have improved reporting (2006).

It is therefore clear that a pooled meta-analysis needs to be made to determine if any change has occurred from 2004 onwards. Alternatively, one could analyse trials published from 2009 onwards and include this in the current dataset.

6.5.5 Poor reporting in Paediatric trials

This study found significantly poor reporting of trials in children with epilepsy. A literature search did not find any studies that used the CONSORT statements to analyses paediatric studies. Items that were poorly reported included definition of adverse events and details of presentation of statistical analysis and if the results were presented separately in each arm. Poor reporting of these items therefore introduces bias in trials in the paediatric age group.

Drugs used in children were usually drugs which were trialled in adults and are currently used as an off-license indication New EU legislation makes financial incentives for drug companies to perform clinical trials for the paediatric population with similar incentives provided by the FDA (EU regulation No 1902/2006). Therefore, it is predicted that the number of paediatric clinical trials is likely to increase as drug companies would need to provide data on children to obtain a drug license. Therefore, new regulation is needed to ensure that the quality of harms reporting is on par with trials performed in adults.

6.5.6 Quality of harms in sections of the trial report

There was marked heterogeneity in reporting of harm outcomes. This study showed that the reporting of harms in the results section was better than the methods section. The methods section included CONSORT items 3 to 12 and the average percent of items met, ranged from 7.2% to 76.3%. If one did not include the timing of AE as an item, it is clear that harms in methods section is relatively poorer in compared to harms reporting in results section. Such heterogeneity is reported in other studies as well (Smith et al 2008).

Items that were reported best were providing denominators for AE (78.3%) and the item reported the poorest, was handling of recurrent adverse events (7.2%). The CONSORT Statements recommend that any additional harms data can be presented as an appendix or a webpage. Only two trials published data on an additional webpage.

It was noted that 75% of epilepsy trials provided a table of harms. This is a very good figure compared to studies in other areas like hypertension where Bagbul & Kirkham (2012) reported a figure of 49% of trials provide an AE table. A table of harms is a useful addition to a trial report as it allows a reader to quickly make judgments on harms and if a trial is to undergoes meta-analysis this data would be very valuable if raw data was not available.

Withdrawal due to adverse events is a useful measure of tolerability; the results showed that 71% of all trials reported withdrawals. There was no difference in the subgroups for reporting of withdrawal data. Other studies that examined withdrawal data found similar rates of reporting. Byrant found the 29% of human growth hormone trial report withdrawals data whereas Capili found 70% of acupuncture trials report withdrawal data (Byrant et al 2002) (Capili et al 2010). Therefore, one can thus conclude that withdrawal data is reported well in epilepsy trials compared to other therapeutic areas. This is an important finding as tolerability measures are commonly incorporated in systematic reviews.

6.5.7 Is Journal space a limiting factor?

The CONSORT recommendations state that harms outcomes should not be published in a separate paper as this may prevent readers having a balanced view of efficacy and harms. The statements recognize that editors are under pressure to conserve manuscript length. The statements do not provide recommendations on how much of journal space should be devoted to this. They recommend a table for harms may save journal space. The analyses presented here showed that the mean percentage of journal space for harms outcomes was 26.8% of the results section. This ranged from 0% where no harms were discussed to 70% in one article. A correlation between percentage of document for harms and CONSORT Score was positive with an R-value of medium strength ($r = 0.42$) (fig 46). One hundred and fourteen trials out of 152 (75%) used a table to describe adverse events. This compared to other areas is significantly greater suggesting that journal have limited space for harms in the text and prefer to display this data as a table.

6.5.8 Other miscellaneous aspects of reporting

Trials may not report every AE and trials report adverse events above a certain threshold. Typically, this is 5 to 10% of all adverse events. This means that if an AE is a relatively infrequent in the trial population, then it will not be reported. Despite this threshold, one would expect a large list of discrete adverse events in trial reports. This study found that 54% of trials did not report the thresholds and 46% did. Forty-one trials reported harms above a > 10% threshold and 29 trials reported harms above a > 5% threshold.

Eight trials did not report any discrete adverse events. The median number of discrete adverse events reported per trial was 9. The maximum number of discrete adverse events was reported in one trial that reported 28 discrete adverse events. There was a weak positive correlation between CONSORT score and number of adverse events, Pearson's R was 0.20 (fig 47).

The CONSORT statements recommend that priming methods may improve reporting. The study by Gilliam et al suggest that using the AEP provided priming for patients subsequently improving reporting of harms in clinic. Only eight trials out of 152 reported priming methods.

Means and descriptive statistics regarding harms were mentioned in 81% of trials. This on the face of it is indicative of good reporting across studies.

The occurrence of deaths in a trial or if no deaths occurred was reported in only 57 trials. Deaths if they occur or not is an important issue that needs reporting explicitly. A recent analysis carried out by Earley et al showed 27% of trials out of 500 published in clincialtrials.gov mentioned deaths, these were reported in either participant flow or primary and secondary outcomes (Earley et al 2013). Deaths were reported crudely in their study and they recommend that crude number of deaths and time to event rates be made mandatory in trial reporting. Trials that do not report deaths may have difficulty in obtaining a licence.

Severity and grading of harms was reported in nearly half of the studies (47.3%) and this was more likely to be reported in commercially funded studies. Also serious adverse events were better reported in commercially funded studies than non-commercially funded studies.

A significant number of trials report harm descriptively and this is what the CONSORT statements recommend as a minimum requirement However, the analyses presented here found 20% of trials report harms as a time to event outcome using graphical or Kaplan Meir curves. This is an important outcome measure of harms. One example of how Kaplan Meir curves have been critical is illustrated with celecoxib and rofecoxib in the risk of cardiovascular events (Mukherjee et al 2001). The use of these metrics highlighted the risk of long-term adverse events and led to withdrawal of these drugs from the market.

6.6 Comparison with reporting of harms in Systematic reviews

Zorsela et al evaluated the reporting of harms in systematic reviews. They found similar level of poor reporting of harms in Cochrane reviews. They included trials between 2008 and 2010 and they identified 309 reviews for inclusion. The CONSORT guidelines were not used for this study but a similar guideline called the PRISMA statement (Zorsela et al 2014). They found that the reporting of the methods section was good in only 40% of systematic reviews, only 50% of reviews reported harms adequately in the results section where the proportions of good reporting was higher in the title, abstract, introduction and discussion section was 70%, 60%, 75% and 80% respectively. These proportions are similar to the results in this study.

6.7 Methodology limitations

This work is the first in the reporting of harms in RCTs of AEDs. However, there are a number of limitations.

- For selection of studies involving two reviewers to select studies for inclusion reduced bias. Cohen's Kappa was used to quantify the level of agreement

between reviewers, however this method does not completely eliminate ascertainment bias.

- Removing the headings and authors from printed copies of included trials could have reduced ascertainment bias.
- There were problems in interpretation of some items in the statements and whether some items were relevant for epilepsy trials. For example, in the statistical section recommendations number 5 states that authors should describe the development of Quality of life and harms scales used. It was noted that the reporting of this was poor but it was decided to keep this recommendation. Conversely, the CONSORT recommendations state that subgroups analysis when present for harms data should be reported. From previous experience of trials reporting this item was not included as very few trials report this Therefore this was excluded this from the checklist by mutual agreement.
- Some studies like Mahinbakht et al used only 10 CONSORT items in their checklist and others used 44 items (Kiehna et al 2011) using the CONSORT checklist use only 10 items where as others used 43. The selection of CONSORT items used in this study was arrived after several discussions with team members and a final checklist was approved. After the writing of this work a number of additional items could have been included but it is expected not to have changed to results significantly (Shukralla et al 2011).
- The CONSORT recommendation number 10 states that trials should " .provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability and other sources of information on harms". For this recommendation, a checklist of four items was created. How these are interpreted is subject to individual biases, which would be difficult to overcome despite efforts to reduce this.
- The statistics were not adjusted for multiple comparisons. This could lead to statistically significant results when indeed there may not be one. Nevertheless, the magnitude of the p-values indicates that there is a true difference in the reporting of harms in commercially funded trials and trials between adults and children.

- Several authors use the CONSORT guidelines and others have used checklists as benchmarking tools to compare trials (Plint et al 2001). However, the checklist and the CONSORT statements are not validated as a scoring system. The original authors of the CONSORT checklist did not envisage that they would be used as a benchmarking tool but rather as a guide for clinicians in helping them understand clinical trials better.

6.8 CONCLUSIONS

- Reporting of harms in RCTs of antiepileptic drugs is poor and this has not improved since the publication of the CONSORT statements
- A good predictor of poor reporting is if the study is a non-commercial study or a paediatric study
- Journal of publication is not a predictor of harms reporting in this study
- Journals that endorse CONSORT are more likely to report harms better
- Poor reporting practices could lead to erroneous and biased reviews

6.9 Recommendations for improving the reporting of harms in RCTs of AEDs

- Increased awareness of the CONSORT guidelines
- Greater uptake of the CONSORT guidelines by journal editors
- Greater involvement of authors of commercially funded studies in the writing of the content of trials reports as they may not be directly involved in the drafting of reports

Chapter 7

Lacosamide: Systematic Review and Meta-analysis

7.1 INTRODUCTION

The reporting of harms in randomised controlled trials is poor as demonstrated in the previous chapter. This is also demonstrated in other studies that show no change in reporting since the publications of the CONSORT guidelines. Poor reporting of trials could have an adverse effect on systematic reviews of clinical trials. Data for reviews are usually obtained from unpublished data, but when such data is not available, then reviewers have to obtain data from the published reports. It is also established that poor outcome reporting can lead to inaccurate estimates in systematic reviews (Kirkham et al 2009).

Lacosamide is a new drug developed by UCB for the treatment of partial epilepsy in 2008. The FDA and EMEA approved a licence for its use in patients with partial epilepsy but not neuropathic pain. Lacosamide is available in tablet, syrup and intravenous formulations. Its intravenous use allows it to be given to patients who are intolerant of oral intake or it can be used to top up an oral dose if patient cannot take it via that route (Biton et al 2008). In clinical practice lacosamide is started at 100mg once a day and gradually increased up to 400mg at weekly increments. The maximum licenced dose is 400mg once a day but some clinicians have used up to 600mg once day (Novy et al 2011). Lacosamide is available as a tablet from in 200mg, 400mg and 600mg doses and is available as an intravenous preparation. The pharmacology of lacosamide was discussed in chapter one.

Lacosamide does not need any dose adjustments in patients with mild or moderate renal failure. A maximum dose of 300mg is used for patients with severe renal failure. Patients with cardiac disease should not be prescribed lacosamide if there is any evidence of AV node dysfunction.

There are current trials underway for its use as monotherapy in partial epilepsy. The use of lacosamide in primary generalised epilepsy is not recommended as it may increase seizure frequency.

This chapter summarises the efficacy and safety of lacosamide by conducting a systemic review, the review will also assess the impact of reporting issues on conducting systematic reviews.

7.2 Aims

This chapter assess the evidence for Lacosamide and its efficacy and safety in treating patients with partial onset seizures. There have been a number of trials of lacosamide and this chapter summarises the evidence for its use in partial epilepsy in a systematic manner.

7.3 **METHODS**

7.3.1 Search strategy.

To be eligible in this review, trials of lacosamide as add-on therapy were searched for.. Clinical trials had to be RCTs to ensure that bias was reduced. An explanation of bias and trials suitable for systematic reviews was explained in chapter. Trials of lacosamide where it was used as monotherapy were excluded. Search strategy for RCTs in lacosamide is shown in appendix H, page 352

At the time of writing, UCB was the sponsor of the clinical trials included in this review. UCB was contacted to provide unpublished data, as this would decrease the risk of publication bias. Any clarification of data provided was made via email to the medical informatics department of UCB. Outcome data and data regarding allocation and concealment and randomisation was obtained directly from study sponsors. Any additional data was obtained from the published trials. Unpublished data was defined as trial data obtained from manufacturers that are not reported in peer-reviewed journals. Experts in the filed were also contacted if there were any other trials of lacosamide for inclusion.

7.3.2 Inclusion and exclusion criteria

These are outlined below

Inclusion criteria

1. Randomised controlled clinical trials of lacosamide
2. Lacosamide used as add-on therapy only
3. Trials in English
4. Placebo or actively controlled trials
5. Double blinded or single blinded studies
6. Minimum period of studies of at least 8 weeks

Exclusion criteria

1. Lacosamide monotherapy trials
2. Observational studies where there was no comparator group

7.3.3 Outcome measures

As outlined in earlier chapters, there are a number of outcome measures that are used in systematic reviews of antiepileptic drugs. The key outcome in epilepsy trials is proportion of patients with ≥50% of reduction of seizures.

7.3.4 Primary outcomes

The key outcome in systematic review of antiepileptic drugs is the 50% reduction in seizure frequency. This is the proportion of people with a 50% reduction in seizure frequency in the treatment period compared to the baseline period. Details of why this outcome was selected as the primary outcome is given in chapter 5 section 5.10.

Seizure frequency is a difficult outcome to analyse in meta-analysis because this would need a comparison of means. Furthermore, seizure frequency is subject to recall bias and other biases., seizure frequency is also not uniformly measured across clinical trials. Proportion of patients with a reduction of seizure frequency on the other hand is less prone to bias.

7.3.5 Secondary outcomes

The following secondary outcome measures were used; seizure freedom, proportion of patients withdrawing from the study, proportion of patients with adverse events, quality of life and cognitive outcomes.

Seizure freedom, this included the proportion of patients who were free of seizures in the treatment period compared to the baseline period. This outcome is not used traditionally in systematic reviews, as the probability of seizure freedom in most clinical trials is rare. It was included in this study as the outcome was reported in a number of lacosamide trials. One study by Zaccara et al (Zaccara et al 2006) suggest that seizure freedom is not traditionally meta analysed in systematic reviews and should be considered but this can be used if the minimum follow up is 6 months and that a typical short study of 12-week duration can still be used to evaluate this outcome. Furthermore, clinicians may be interested in the review of this outcome, as lacosamide would be given to patients with intractable epilepsy.

Treatment withdrawal is the proportion of patients who withdrew for any cause during the treatment period and is the key outcome measure used in systematic reviews. Treatment withdrawal can be due to any cause including adverse events. This has been used in several other Cochrane reviews and is a good marker of tolerability (Zaccara et al 2006).

7.3.6 Adverse Events

A comparison of the proportion of patients that withdrew due to harms was made, the total number of adverse events in each group and finally a comparison of the proportion of patients who experienced the specific adverse events was made. These outcomes were obtained from unpublished data provided from UCB.

Names of adverse events were not altered and synonymous adverse events were not combined. The selected list of adverse events was chosen, as these were common to at least two of the selected trials. Adverse events described in the published literature

were called treatment emergent adverse events. The following adverse events were used:

1. Any adverse event
2. Accidental injury
3. Ataxia
4. Blurred vision
5. Coordination abnormal
6. Diplopia
7. Dizziness
8. Fatigue
9. Headache
10. Nasopharyngitis
11. Nausea
12. Nystagmus
13. Peripheral oedema
14. Rash
15. Somnolence
16. Tremor
17. Upper respiratory tract infection
18. Vertigo
19. Vomiting

Some harms outcomes like ataxia and coordination abnormal may intuitively be synonymous but these were not summated.

7.3.7 Other outcomes

Other outcomes that were included in thesis included quality of life measures and cognitive changes experienced by patients. Quality of life measures included quality of life scores and standardised cognitive scores. These outcomes were presented narratively.

7.3.8 How outcomes are presented

Outcomes will be presented in three domains

1. Efficacy of lacosamide versus placebo
    a. Proportion of patients with a ≥ 50% reduction in seizure frequency
    b. Proportion of patients seizure free during the 12-week maintenance period
2. Tolerability of Lacosamide versus placebo
    a. Proportion of patients having treatment withdrawn during the maintenance period
3. Adverse events

Given clinical trials present outcomes by dose subgroups, all outcomes were presented using the following doses:

- Lacosamide 200mg
- Lacosamide 400mg
- Lacosamide 600mg
- Lacosamide any dose

7.3.9 Participants

Patients included must have epilepsy. These were patients of any age and must have at least one antiepileptic drug. Patients need to have a specified minimum frequency of seizures to be included into the trial. Pregnant patients were excluded and progressive epilepsies were excluded from the study. If patient could not comply with protocols, they were also excluded.

7.3.10 Search Methods

Electronic searches were made for lacosamide trials. One did not need to carry hand searches as the intervention is adequately tagged in MEDLINE. Other searches

included the specialised register contains trial of epilepsy in the Cochrane database. Trials had to meet the following criteria:

1. Trials had to use an adequate method of randomisation
2. Trials had to use a method of blinding
3. Trials had to be of lacosamide
4. Comparator group had to include placebo

To reduce bias in the search strategy and selection of trials, this was carried out by two reviewers and any disagreements were resolved after mutual discussion.

7.3.11 Selection of studies

Selection of trials was carried out by two persons. Any differences were resolved by mutual agreement.

7.3.12 Data extraction

Items of data for systematic reviews include two main categories. The first is data relating to the methodological vigour of selected trials and ascertaining the risk of bias. The second is data relating to results and outcomes. Data was extracted into a data extraction form. A list of subheadings is shown below.

1. Methodological and trial design
2. Patient demographic data
3. Primary and secondary outcome data including harms data
4. Ascertainment of risk of bias
5. Ascertainment of clinical heterogeneity

Two authors extracted data from trials for details of method of randomisation. Methods of allocation concealment, methods of blinding and missing participants. Other data relating to methods included length of the baseline period, length of treatment period and dose of lacosamide used. This data was obtained from the

published reports of trials selected. If this data was not available the trial sponsor was contacted to respond to queries posed to them. UCB were contacted for medical information on details of allocation and blinding as this was not reported in published reports.

7.3.13 Demographic data collection

Demographic data from the published reports and from unpublished data was collected. If there were any disparities, then the unpublished data was used for the item concerned. Items of data included:

1. Participant age
2. Ethnic group of patients
3. Seizure types
4. Seizure frequency
5. Baseline AEDs and/VNS
6. Proportion of patients meeting target dose

Other items of data extracted included the number of patients randomised to each arm, the dose of active intervention in each arm. Proportion of patients in each arm with > 50% reduction in seizure frequency. Proportion of patients withdrawn from each arm. Proportion of patients seizure free. Proportion of patients with treatment emergent adverse events.

7.3.14 **Assessment of risk of bias**

Two reviewers conducted an assessment of the risk of bias. Cochrane risk of bias tables as described in Higgins 2011was used and related incorporated into RevMan 5.0. See earlier chapters for an explanation of this.

The risk of bias was rated as high, low or unclear on six domains, the details of these domains have been explained in chapter five, section 5.16 These domains included randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias. Risk of bias was illustrated using risk of bias matrix.

The ORBIT tool to assess the risk of bias in outcome reporting was also used, details of which were described in chapter five, section 5.16.1

7.3.15 Measures of treatment effect

The majority of the outcomes are categorical in nature and therefore are presented using relative risks. Relative risks were used instead of odds ratios to present measures of treatment effect as it is expected treatment effect sizes will be small and therefore relative risks would provide a better estimate than odds ratios. Quality of life measures were presented narratively as there is no consensus on which measure should be used in systematic reviews and clinical trials are not always consistent in their use off quality of life measures.

7.3.16 Assessment of heterogeneity

Clinical heterogeneity was assessed by comparing the distribution of patient demographics. We used the I^2 statistic to calculate heterogeneity. This was included in RevMan 5.0. If there was no heterogeneity we used the fixed effects model. But we did not plan to carry out subgroup analysis for sensitivity to explore heterogeneity.

7.4 RESULTS

7.4.1 Results of the search

Searches revealed 379 studies pertaining to Lacosamide. Of these only 19 were tagged as randomised controlled trials. Of these only three trials involved patients with epilepsy compared with placebo. The excluded studies were not used.

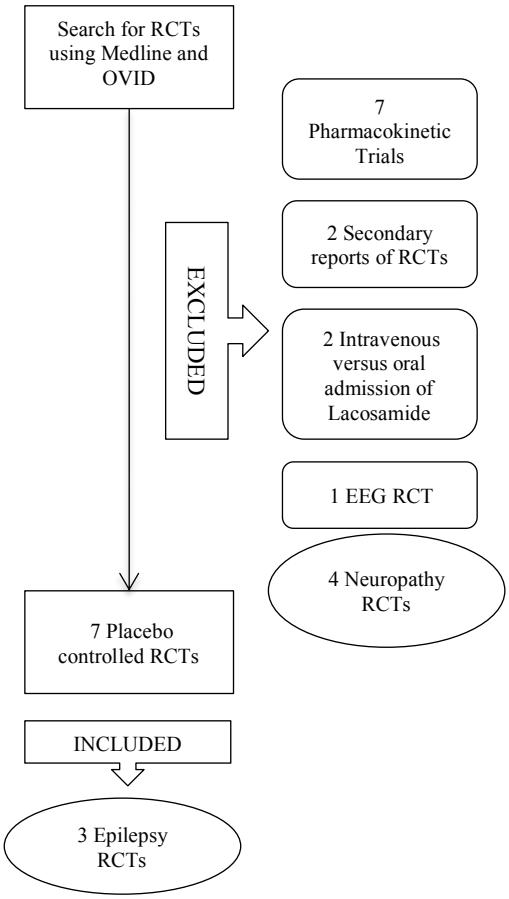


Figure 48 Flow diagram of disposition of studies selected

7.4.2 Excluded studies

Excluded studies are shown in table 38. A total of three studies were included for review. We excluded one trial, which compared rates of infusion of lacosamide, as this did not include a placebo group. We also excluded a study comparing the oral formulation of lacosamide with intravenous lacosamide; this study was excluded, as it did not have a placebo group (Biton et al 2008). Four trials of lacosamide in peripheral neuropathy studies were excluded for this review. Four trials of lacosamide with pharmacokinetic data were excluded. There are no studies that are awaiting review.

7.4.3 Included studies

Three studies were included for review. All three studies were sponsored by UCB. The trials were part of a drug development programme to gain a licence for Lacosamide (Ben-Menachem 2007, Halasz 2009 and Chung 2010). A list of excluded studies is

shown in table 38 and the included studies is shown in table 39. Trials details and characteristics of included studies are shown in table 41. Details of outcome reported in selected trials are shown in table 42. Table 40 highlights the key outcome measure results.

The first study by Ben-Menachem was reported in 2007 (Ben-Menachem et al 2007). This was a phase 2b study comparing lacosamide to placebo in patients with focal epilepsy. The other two studies were phase 3 studies by Halasz and Chung (Halasz et al 2009)(Chung et al 2010). A total of 1311 patients were randomised in all three studies. Two hundred and seventy patients were allocated to 200mg of lacosamide. Four hundred and seventy one were allocated to 400mg of lacosamide and three hundred and sixty six patients were allocated to 600mg of lacosamide. One hundred and ninety patients were allocated to placebo. All three studies included data on the proportion of patients free from seizure during the 12-week maintenance period. In one study patients were on one or two AEDs (Ben-Menachem et al 2007), in the other two trials up to three AEDs were used by patients. (Halasz et al2009)(Chung et al 2010). The most common AEDs were carbamazepine (35%), lamotrigine (31%), levetiracetam (29%), valproate (24%), topiramate (22%), oxcarbazepine (18%) and phenytoin (14%).

Study	**Reason for exclusion**
Biton 2005	These studies compared intravenous lacosamide with oral lacosamide. There was no placebo group, therefore they were excluded
Biton 2008	
Jatuzis 2005	Pharmacokinetic studies
Jatuzis 2006	
Kalvianinen 2007	
Raosenfeld 2005	
Rauck 2007	These studies compared oral lacosamide with placebo in patients with painful diabetic neuropathy
Shaibani 2009	
Wymer 2009	
Ziegler 2010	

Table 38 List of excluded lacosamide studies

Study	**Title**	**Reason for inclusion**
Ben-Menachem 2007	Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures	Compared oral lacosamide to placebo in patients with partial epilepsy and was a randomised controlled trial.
Halasz 2009	Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial	
Chung 2010	Lacosamide as adjunctive therapy for partial-onset seizures: A randomized controlled trial	

Table 39 List of included lacosamide studies

Ben Menachem 2007

In this study patients were allocated in a 1:1:1:1 ratio to placebo, Lacosamide 200mg, 400mg and 600mg. the baseline period was 8 weeks with a six week titration period of 100mg/week. A single down titration was allowed of 100mg /week. Maintenance period was 12 weeks.

All patients aged 18-65 years of age. Patients needed to have had seizures for at least 2 years. 93% of patients were Caucasian and 82% of patients achieved the target dose.
Lacosamide was superior to placebo for the 400mg and the 600mg dose; the 200mg (median 20% of doses) dose was not significant. The 400mg and 600mg doses included 39% and 40% of doses respectively.

Halasz 2009

This was a phase 3 randomised placebo controlled trial evaluating the 200mg and 400mg dose of lacosamide compared to placebo. Patients here were allocated in a 1:1:1 ratio to placebo, 200mg lacosamide and 400mg lacosamide. Again the baseline period was 8 weeks and the titration period was 4 weeks. Titration rate was the same as the other trials of 100mg/week. The treatment period was 12 weeks.
Patients were adults with focal epilepsy. Here 99% of patients were Caucasian. In this study, 38 patients were excluded after screening and 61 patients were not randomised.

Chung 2010

This was a phase 3 randomised placebo controlled trial evaluating 400mg and 600mg dose of lacosamide compared to placebo. Patients were allocated to 1:2:1 to placebo, 400mg Lacosamide and 600mg lacosamide. The baseline period was similar to other studies was 8 weeks and titration period was 6 weeks and treatment phase was 12 weeks. Patients recruited were adults with focal epilepsy who had failed on at least 2 AEDs. In this trial 81.1% of patients reached the target dose. This trial demonstrated efficacy of the 400mg and 600mg doses, as the 200mg dose was not significant in

above two trials. Seizure types were not discussed in Chung et al but was discussed the other two trials (2010).

7.4.4 Comparison of primary outcome measures

The three trials reported similar responder rates in the intention to treat analysis (ITT) for identical drug doses. There was very little difference in the 200mg, 400mg and 600mg doses across three trials. On the other hand for the per-protocol (PP) analysis we found that the 400mg dose had a 49.4% responder rate in Ben-Menachem but only 40% in Chung, reasons for this could be due to differences in the trial population (table 40).

	Dose	Responder rate IIT analysis	Responder rate PP analysis
Ben Menachem 2007	Placebo	22%	21.2%
	200mg	32.7% (p = 0.08)	38.1% (p <0.05)
	400mg	41.1% (p <0.05)	49.4% (p <0.05)
	600mg	38% (p <0.05)	49.2% (p <0.05)
Halasz 2009	Placebo	25.8%	27.5%
	200mg	35.0% (p = 0.07)	35% (p = 0.19)
	400mg	40.5% (p <0.05)	46.3% (p <0.05)
Chung 2010	Placebo	18.3%	18.4%
	400mg	38.3% (p <0.05)	40.0% (p <0.05)
	600mg	41.2% (p <0.05)	50.9 (p <0.05)

Table 40 Comparison of Primary Outcome measures (ITT vs. PP analysis)

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7.4.5 Clinical Heterogeneity

Minimal clinical heterogeneity was found between studies. Mean ages were similar between groups. The distribution of age groups and seizures types were similar across all three trials. There were less Caucasians patients recruited in Chung 2010 compared to the other two trials. Demographics are shown in table 41. We deemed that there is little clinical heterogeneity and therefore trials are evaluable for systemic review.

7.4.6 Risk of outcome reporting bias from ORBIT tool

Ben-Menachem (2007) was low risk in outcome reporting as all the outcomes that were planned were presented in the trial reports. This was true for the primary outcomes, secondary outcomes and additional outcomes as well.

However, Halasz (2009) and Chung (2010) analysed quality of life outcomes, they did not report these in the published manuscript. Instead theses were published in abstracts and posters where data from all three trials were pooled together (Borghs et al 2010). Therefore, Halasz and Chung were deemed to have high risk of outcome reporting bias. Nevertheless, when assessing the overall risk of bias for purposes of this review it was deemed that the overall risk of bias is low. No trial reported the absolute change in seizure frequency from baseline. Determining if there is outcome reporting bias is important as if this exists then the effect sizes need to be interpreted with caution if outcome reporting affects the primary or secondary outcomes. In this review, the risk is low as the incomplete outcomes are quality of life measures.

7.4.7 Risk of bias summary

Using the unpublished data, one was able to obtain details of selection of patients and details of treatment allocation. For all three trials, it was deemed that allocation was adequate. Also, random sequence generation was also adequate and was done remotely by a computer for all three trials (fig 52 and 53).

Patients and trial assessors were blinded to treatment allocation and which treatments they received. Therefore, the risk of bias was low.

Incomplete outcome reporting is where the outcomes are poorly reported. Here for the items that were of key interest for this review was good.

Some of the items discussed on page 190 with regards to the ORBIT tool were pertaining to the non-reporting of quality of life measures that were discussed in conference abstracts and not the published trials. The outcomes in question were the Patient's Global Impression of Change score (PGIC) and the Seizure Severity Scale (SSS). Since these outcomes are quality of life outcomes, it was therefore deemed that the risk of reporting bias was low. These items are not primary or secondary outcomes

in this review. Tables 42 to 43 shows results of judgements made using the ORBIT assessment tool.

Our risk of bias judgement showed that the risk of bias from selection, detection and performance bias was low. Detection and attrition bias was low. The risk of selective reporting bias was low. Outcome reporting bias was low in Ben-Menachem et al for all outcomes reported, but the risk of bias of the other two trials was high for certain quality of life measures. Nevertheless, the overall risk was deemed low, as these outcomes were not included in the analysis.

7.4.8 Other sources of evidence

Posters of lacosamide presented at epilepsy meetings were used. These reported data not found in the published trial reports or unpublished data. This included a pooled analysis of lacosamide for quality of life measures (De La Loge et al 2009). A list of all outcomes is shown in table 42.

7.4.9 Funnel plots

Funnel plots for the three main outcomes were made. These plotted the standard error of the log of relative risk against the relative risks. In the absence of bias these should show a symmetrical shape of a funnel. These are shown in the diagrams below (fig 49 to 51). The funnel plots do not indicate a risk of reporting bias based on this analysis.

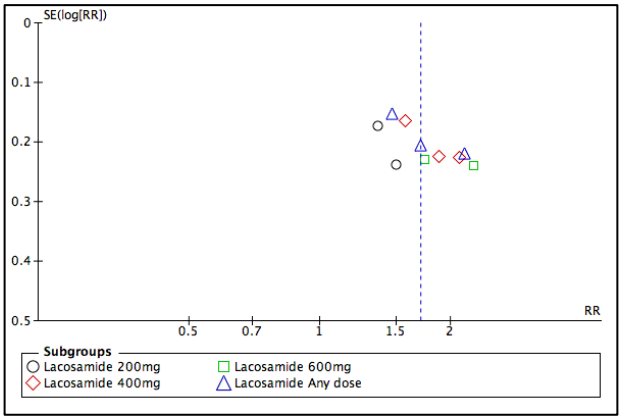

Figure 49 Funnel plot of comparison: Efficacy of lacosamide versus placebo: Proportion of patients with a 50% or greater reduction in seizure control

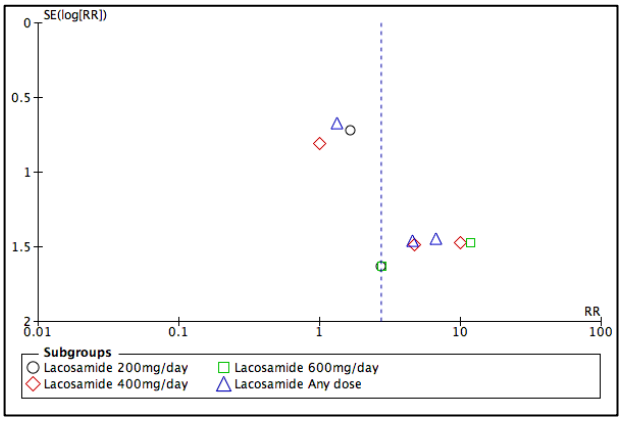

Figure 50 Funnel plot of comparison: Efficacy of lacosamide versus placebo: Proportion of patients seizure free during maintenance period

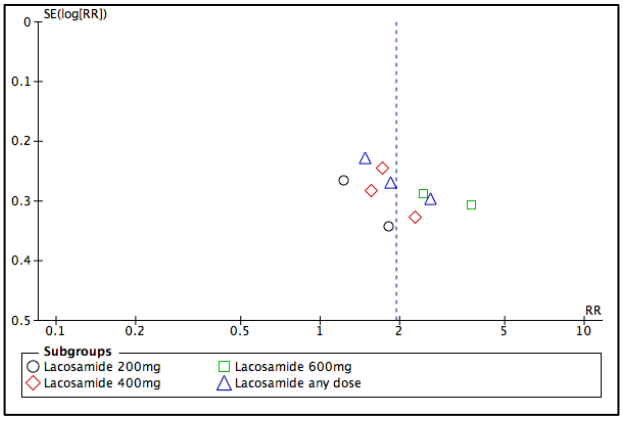

Figure 51 Funnel plot of comparison: Tolerability of lacosamide: proportion of patients who have treatment withdraws during maintenance period

Table 41 Characteristics of lacosamide studies

Patient characteristics	**Ben-Menachem 2007**				**Halasz 2009**			**Chung 2010**		
Number of patients randomised	418				485			405		
Dose	Placebo	200mg	400mg	600mg	Placebo	200mg	400mg	Placebo	400mg	600mg
Age (mean years) Range	38.8 19-66	39.9 18-65	41.2 18-68	39.4 18-64	38.5 17-63	36.9 16-66	37.9 16-70	38.1 16-61	39.1 17-71	36.8 16-69
Sex (%)	M 48 F 52	M 43 F 57	M 49 F 51	M 42 F 58	M 55.8 F 44.2	M 44.4 F 56.6	M 51 F 49	M 47.1 F 52.9	M 51 F 49	M 48.5 F 51.2
Race (%) White Asian Black Other	 91 0 6 3	 92 2 4 3	 93 0 5 3	 95 0 2 3	 99.4 0.6 0 0	 99.4 0 0.6 0	 98.7 1.3 0 0	 81.8 1 8.2 1	 81.4 1.6 7 1	 82.5 1.7 5 2
Mean time to diagnosis (years)	24.6	25.1	24.7	23.6	21.1	22.9	22.8	25.4	24.5	23.4
Seizure types (%) Simple partial Complex partial 2° generalised	 34 86 75	 45 94 74	 38 87 71	 47 91 66	 37.4 84.7 79.8	 41.1 87.1 76.7	 36.5 91.8 79.9	Not reported		
Baseline partial onset seizure frequency per 28 days	11-13 seizures, no data for individual dose				15	11.5	16.5	9.9	11.5	10.3
AEDs	1 to 2 concomitant AEDs				1 to 3 concomitant AEDs			1 to 3 concomitant AEDs		
Randomisation scheme	1:1:1:1				1:1:1			1:2:1		
Duration Baseline phase Titration phase Maintenance phase	 8 weeks 6 weeks 12 weeks				 8 weeks 6 weeks 12 weeks			 8 weeks 6 weeks 12 weeks		

Table 42 Outcomes reported in included studies

	Ben Menachem 2007	**Halasz 2009**	**Chung 2010**
Outcomes Common to all studies	• Change in seizure frequency per 28 days from baseline in ITT and PP population • Responder rate, defined as the proportion of patients with a greater than or equal to 50% reduction in seizure frequency in both the ITT and PP population (called the 50% responder rate • Responder rate 75% • Proportion of patients seizure free throughout the 12 week maintenance period • Percentage change in seizure free days compared to baseline • Adverse events • Serious Adverse events • Proportion of patients withdrawn due to adverse events • Proportion of patients meeting target dose • Pharmacokinetic outcomes • Quality of life outcome: QOLIE-31		
Other Outcomes	Any adverse events	PGIC quality of life outcome SSS quality of life outcome Note: Any adverse event was not reported in this trial	• Responder rate by seizure type • Change in seizure frequency per 28 days from baseline by seizure type • Number of patients seizure free during the maintenance period calculated in the ITT method • PGIC and SSS quality of life outcomes Note: Any adverse events was not reported in this trial

Patient's Global impression of change score (PGIC); Seizures severity scale (SSS); Quality of life in Epilepsy (QOLIE-31)

Table 43 ORBIT assessment tool results

Trial ID	**Primary Outcome** ≥ 50% reduction in seizure frequency	**Other Outcome** Treatment withdrawal	**Other Outcome** Adverse events	**Other Outcomes** Quality of life Measures	**Additional Outcomes** Percentage change in seizure frequency from baseline	**Additional Outcomes** Absolute change in seizure frequency from baseline	**Additional Outcomes** ECG, physical neurological examinations and laboratory tests	**Pharmacokinetic outcomes**	**Judgement of risk of bias**
Ben Menachem 2007	Measured Presented Analysed Also reported ≥ 75% reduction in seizure frequency	Measured Presented Analysed	Measured Presented Analysed Any adverse event Also reported proportion of patients with dose reduction due to AE Threshold of reporting > 5%	Measured Presented Analysed QOLIE-31 only	Measured Presented Analysed	Not measured	Measured Presented Analysed	Measured Presented Analysed	Low risk of bias
Halasz 2009	Measured Presented Analysed	Measured Presented Analysed	Measured Presented Analysed Threshold of reporting > 5%	Measured only QOLIE-31 PGIC SSS	Measured Presented Analysed	Not measured	Measured Presented Analysed	Measured Presented Analysed	High risk of bias as quality of life outcomes measured but not reported. These were presented elsewhere
Chung 2010	Measured Presented Analysed Also reported ≥ 75% reduction in seizure frequency	Measured Presented Analysed	Measured Presented Analysed Threshold of reporting > 10%	Measured only QOLIE-31 PGIC SSS	Measured Presented Analysed Also presented reduction in seizure frequency by seizure type	Not measured	Measured Presented Analysed	Measured Presented Analysed	High risk of bias as quality of life outcomes measured but not reported. These were presented elsewhere

Table 44 Risk of bias assessments using the ORBIT assessment tool

Study	Outcome	Risk of Bias in Outcome reporting	Overall Judgement
Ben Menachem 2007	1. ≥ 50% reduction in seizure frequency 2. ≥7 5% reduction in seizure frequency 3. Treatment withdrawal 4. Adverse events 5. Any adverse event 6. Proportion of patients with dose reduction due to AE 7. QOLIE 31 8. Percentage in seizure frequency from baseline	1. No risk 2. No risk 3. No risk 4. No risk 5. No risk 6. No risk 7. No risk 8. No risk	No risk of bias
Halasz 2009	1. ≥ 50% reduction in seizure frequency 2. Treatment withdrawal 3. Adverse events 4. QOLIE 31 5. PGIC 6. SSS	1. No risk 2. No risk 3. No risk 4. High risk 5. High risk 6. High risk	Risk of bias uncertain due to some outcomes having low risk and some outcomes having high risk. High risk because items were reported in published conference abstracts and posters but not in unpublished reports provided by UCB. Outcome any adverse event not reported
Chung 2010	1. ≥ 50% reduction in seizure frequency 2. Treatment withdrawal 3. Adverse events 4. QOLIE 31 5. PGIC 6. SSS	1. No risk 2. No risk 3. No risk (>10% threshold but does not affect ORBIT) 4. High risk 5. High risk 6. High risk	Risk of bias uncertain due to some outcomes having low risk and some outcomes having high risk High risk because items were reported in published conference abstracts and posters but not in unpublished reports provided by UCB. Outcome any adverse event not reported

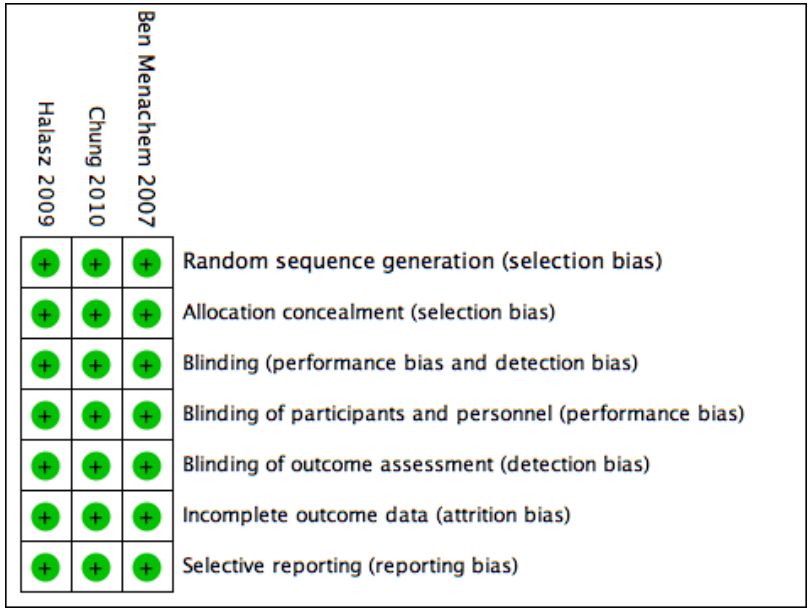

Figure 52 Risk of bias summary. Review authors judgements about each risk of bias item for each included study: Illustrating the low risk of bias across trials for all items

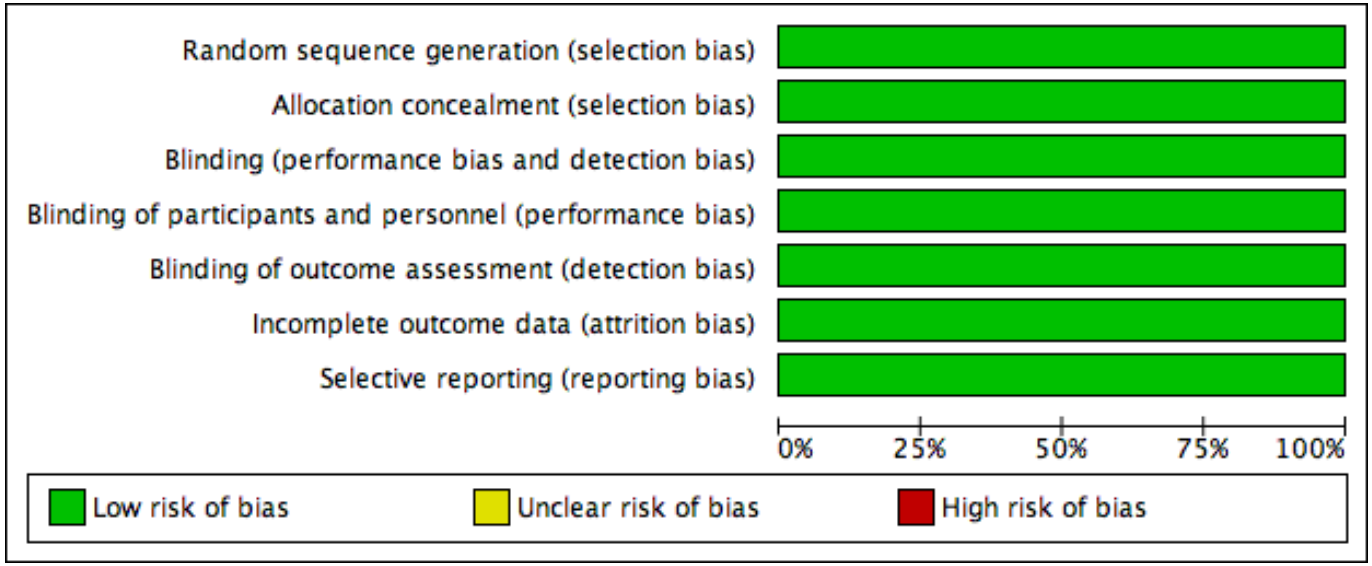

Figure 53 Risk of bias graph. Authors judgement about the risk of bias item presented as percentage across all included studies. Illustrating the low risk of bias across all items

7.4.10 Efficacy outcomes

7.4.10.1 Responder rate (proportion of patients with a > 50% reduction in seizure frequency)

Fifty percent reduction rate in seizure frequency was analysed for all three trials. There was an incremental increase in relative risks as the dose of lacosamide increased. Heterogeneity and not significant was an I^2 of 0% for all three doses and 5% for any dose of lacosamide (fig 54 page 204).

Summary measures were calculated for 200mg 400mg, 600mg and any dose of lacosamide. For the 200mg dose the relative risks for two trials ((Ben-Menachem et al 2007) and (Halasz et al 2009)) included unity and therefore the relative risks were not significant. However, when these two trials were summated the relative risk was 1.41 (95% CI of 1.07 to 1.85). Therefore, the summary measures reached statistical significance in favour of lacosamide. Summary measures for the 400mg and 600mg doses were 1.80 (95% CI 1.43 to 2.25) and 1.98 (95% CI 1.42 to 2.73) respectively. For any dose of lacosamide the relative risk was 1.70 with a 95% CI of 1.38 to 2.10.

The other outcome we used was the proportion of patients seizure free during the maintenance phase of three trials. Once again, the levels of heterogeneity were low for analysis conducted.

7.4.10.2 Seizure freedom

Proportions of patients seizure free when taking lacosamide were analysed (fig 55 page 204). All three trials evaluated patients for 12 weeks. Again, the outcomes were subgroup by dose. For the 200mg dose the summary effect was in favour of lacosamide but due to wide confidence intervals it was not statistically significant. The relative risk of seizure freedom on lacosamide was 1.8 compared to placebo. (95% CI of 0.50 to 6.57). For the 400mg dose, the relative risk was 2.70 (95% CI of 0.85 and 8.56). The resistive risk for the 600mg dose was 7.09 (95% CI of 0.9 to 55.7). For any dose of lacosamide the relative risk of seizure freedom compared to placebo was 2.50 (95% CI 0.85 to 7.34). Overall the risk of seizure freedom was higher in the

lacosamide group but this was not statistically significant due to the wide confidence intervals.

7.4.11 Tolerability outcomes

Tolerability of lacosamide was assessed using the proportion of patients that withdrew due to adverse events (fig 56 page 205). This is a generic measure of overall tolerability. This too was sub-grouped by dose. For the 200mg dose the risk of withdrawing due to adverse events was 1.43 (95% CI of 0.95 to 2.15). Therefore, this was not statistically significant compared to placebo.

For the 400mg the overall relative risk of withdrawals due to harms compared to placebo was 1.79 with a 95% CI of 1.31 to 2.46. This therefore was statistically significant. Furthermore, for the 600mg dose the risk of withdrawal due to harms was 3.04 (95% CI of 2.02 to 4.59).

When all doses were considered the overall relative risk of lacosamide was 1.88 with a 95% CI of 1.40 to 2.52.

7.4.11.1 Any Adverse Event

The proportions of patients with any adverse events were analysed (fig 58 page 205). This outcome was reported in Ben-Menachem and not in the other two trials. For the 200mg dose the risk of having any adverse event compared to placebo was 1.13 (95% CI 0.96 to 1.33. This increased to 1.15 (95% CI of 0.98 to 1.35) for the 400mg dose and 1.32 (95% CI of 1.15 to 1.52) for the 600mg dose. For any dose of lacosamide the relative risk of having any adverse event was 1.20 (95% CI of 1.04 to 1.38) compared to placebo.

7.4.11.2 Serious Adverse Events

Serious adverse events are those that are which are unexpected or cause serious harm to patients (fig 57 page 205). The risk of serious adverse events was not different in to trials; Ben-Menachem 2007 and Chung 2010 with relative risks of 1.21 (95% CI of

0.41-3.44) and 1.73 (95% CI of 0.51-5,39) respectively. This was not the case for Halasz (2009) with at least twice more serious adverse events in this trial. The relative risk was 2.36 (95% CI of 1.0 to 5.39). No deaths were reported in any of the trials. When all serious adverse events were meta-analysed, the relative risk of serious adverse event was 1.78 (95% CI of 1.02 to 3.12). This risk of serious adverse events is surprising given that Halasz used the lower doses of lacosamide.

Also, paradoxically, the relative risk of serious adverse events was higher in the 200mg and 400mg dose compared to the 600mg dose. The relative risk was 2.0 for the 200mg dose (95% CI of 1.0 - 4.02) and 1.97 for the 400mg dose (95% CI of 1.07 - 3.63). The risk of serious adverse events for the 600mg dose was 0.74 (95% CI of 0.26 and 2.07).

7.4.12 Adverse Events

Adverse events that were reported in patients taking lacosamide and placebo included: accident not otherwise specified (NOS); ataxia; blurred vision; co-ordination abnormal; diplopia; dizziness; fatigue; headache; nasopharyngitis; nausea; nystagmus; peripheral oedema; rash; somnolence; tremor; upper respiratory tract infection (URTI); vertigo and vomiting. The relative risk of some of the adverse events was significantly higher in magnitude compared to the efficacy measures. Differences in reporting of adverse events are shown in the table 45 on page 197.

	Ben-Menachem 2007	Halasz 2009	Chung 2010
Accidental Injury	Reported		
Ataxia	Reported		
Blurred Vision	Reported		Reported
Coordination abnormal		Reported	Reported
Diplopia	Reported	Reported	Reported
Dizziness	Reported	Reported	Reported
Fatigue	Reported	Reported	
Headache	Reported	Reported	Reported
Nasopharyngitis		Reported	
Nausea	Reported	Reported	Reported
Nystagmus	Reported		Reported
Peripheral oedema			Reported
Rash			Reported
Somnolence	Reported		Reported
Tremor			Reported
Upper resp. tract infection	Reported		
Vertigo		Reported	
Vomiting	Reported	Reported	Reported

Table 45 List of adverse events reported in lacosamide studies; epilepsy trials

7.4.12.1 Ataxia

The risk of ataxia increased with increasing dose of lacosamide (fig 60 page 207). The risk of ataxia for any dose of lacosamide was 3.02 (95% CI of 1.49 to 6.14). The risk was even higher with 600mg dose of lacosamide (relative risk of 4.38 with 95% CI of 2.10 to 9.17) and the relative risk of ataxia was 2.91 for the 400mg dose of lacosamide (95% CI of 1.35 to 6.27).

7.4.12.2 Blurred vision

The relative risk of blurred vision increased with increasing dose of lacosamide (fig 61 page 207). The risk was not significant compared to placebo for the 200mg dose; relative risk was 0.73 (95% CI of 0.2 to 2.62). The risk increased to 2.91 (95% CI of 1.35 to 6.27) for the 400mg dose and 4.38 (95% CI of 2.10 to 9.17) for the 600mg dose. The overall risk of blurred vision was 3.02 (95% CI of 1.49 to 6.14).

7.4.12.3 Coordination abnormal

The risk of coordination abnormal increased with increasing dose of lacosamide (fig 62 page 208). This was significant for the 400mg, 600mg and any dose of lacosamide. These were 6.13 (95% CI of 1.92 to 19.51) for the 400mg dose; 5.90 (95% CI of 1.34 to 25.93) for the 600mg dose and 6.12 (95% CI of 1.94 to 19.34) for any dose of lacosamide.

7.4.12.4 Diplopia

The risk of diplopia was significant for all doses of lacosamide and for any dose of lacosamide (fig 63 page 208). Relative risk for diplopia was 4.10 (95% CI of 1.41 to 11.95) for the 200mg dose; 5.18 (95% CI of 2.40 to 11.18) for the 400mg dose; 6.61 (95% CI of 2.63 to 16.61) for the 600mg dose of lacosamide. The relative risk of diplopia for any dose of lacosamide was 5.29 (95% CI of 2.49 to 11.24).

7.4.12.5 Dizziness

The relative risk of dizziness compared to placebo increases with increasing dose of lacosamide (fig 64 page 209). The risk of dizziness was 2.26 (95% CI of 1.34 to 3.79) for 200mg of lacosamide; 3.33 (95% CI of 2.27 to 4.88) for the 400mg dose of lacosamide; and 5.04 (95% CI of 3.29 to 7.72) for the 600mg of lacosamide. The relative risk for dizziness for any dose of lacosamide was 3.53 (95% CI of 2.46 to 5.07).

7.4.12.6 Fatigue

This harm outcome was reported in Ben-Menachem (2007) and Halasz (2009) but was not reported in Chung (2010) (fig 65 page 209). The relative risk of fatigue was significant for the 600mg dose of lacosamide. The risk was 3.84 (95% CI of 1.51 to 9.80). The risk of fatigue for any dose of lacosamide was 2.11 (95% CI of 1.12 to 3.97).

7.4.12.7 Nasopharyngitis

This was reported in Halasz only (2009). All relative risk estimates included unity therefore the risk of nasopharyngitis was not significant compared to placebo for all doses of lacosamide (fig 67 page 210).

7.4.12.8 Nausea

The relative risk of patients with nausea increased with increasing dose (fig 68 page 211). The 200mg dose was not significant. The relative risk of nausea was 2.46 (95% CI of 1.43 to 4.23) for the 400mg dose; 2.44 (95% CI of 1.36 to 4.38) for the 600mg dose. The overall relative risk of nausea was 2.37 (95% CI of 1.44 to 3.91).

7.4.12.9 Vertigo

The relative risk of vertigo was 3.67 (95% CI of 1.04 to 12.9) for the 200mg dose and 3.42 (95% CI of 0.96 to 12.19) for the 400mg dose (fig 75 page 214).

7.4.12.10 Vomiting

The relative risk of vomiting increased with increasing dose (fig 76 page 215). The risk of vomiting was 2.52 (95% CI of 1 to 6.34) for the 200mg dose; 2.95 (95% CI of 1.56 to 5.6) for the 400mg dose and 3.64 (95% CI of 1.70 to 7.78).

7.4.12.11 Adverse events with non-significant relative risks

A number of adverse events were not significantly different to placebo as the relative risks included unity. These were: accidental injury NOS (fig 59 page 206), headache (fig 66 page 210), nasopharyngitis (fig 67 page 210), Nystagmus (fig 69 page 211), peripheral oedema (fig 70 page 212), rash (fig 71 212), somnolence (fig 72 page213), tremor (fig 73 page 213) and upper respiratory tract infection (fig 74 page 214).

8.5 DISCUSSION

Lacosamide is a novel drug licensed for use in focal epilepsy. Unlike other AEDs, lacosamide increases slow inactivation of sodium channels. With a new mechanism of action, it was hoped that lacosamide would have a beneficial effect in patients with focal epilepsy.

The efficacy and safety of lacosamide was studied in three regulatory trials. In two of these (Ben-Menachem 2007 & Halasz 2009), the 200mg dose was not statistically significant when compared to placebo. However, the 200mg dose was significantly different compared to placebo using the per-protocol analysis. For the 400mg and 600mg doses of lacosamide, there was significant difference between lacosamide and placebo in all three trials.

Responder rates also varied in the three trials even though they used the same study protocol. Responder rates ranged from 32.7% to 35% for the 200mg dose; 40.5% to 41.2% for the 400mg dose and 38% to 41.2% for the 600mg dose. Despite a trebling of dose from 200mg to 600mg, there were no marked difference in responder rates between doses and this was reflected in the corresponding relative risks. No clear explanation of this is possible and one can speculate that these differences are due to a phenomenon of a significant treatment response to placebo.

This review looked at the efficacy of lacosamide compared to placebo from data obtained from the three controlled trials. The results showed that the effect sizes for the 200mg dose was statistically significant when two trials were combined This is due to larger power in combining both studies and this could detect a change which is possibly present but was not detected in the individual trials. The relative risk of the responder rate was higher in the 400mg and 600mg doses. The relative risks are 1.41 for the 200mg dose, 1.80 for the 400mg dose and 1.98 for the 600mg dose. Relative risks presented here for lacosamide when compared to Cochrane reviews of other AEDs by comparison is smaller. One can hypothesise the smaller relative risks is due to a relatively larger placebo response (Rheims et al 2008).

Seizure freedom as an outcome was included in this review. This outcome is uncommonly used in systematic reviews as it is infrequently reported and the likelihood of patients being seizure free in a 12 week RCT is more likely to be due to random chance. The number of seizure free patients was too small leading to wide confidence intervals, to evaluate seizure freedom we may need longer trial duration.

Markers of tolerability were the proportion of patients who withdrew due to adverse events. Tolerability for the 200mg dose of lacosamide was not different from placebo indicating that lacosamide 200mg was tolerated well. Tolerability for the 400mg and 600mg dose was poorer with increasing risk of withdrawals due to adverse events. Patients with 600mg were about three times likely to stop treatment due to adverse events.

Part of the systematic review process includes an assessment of the risk of bias. The included studies pose a low risk of bias and unpublished data reduced this risk of reporting bias further. It is deemed that there is low risk of bias as most outcomes were reported. There were some quality of life outcomes that were not reported in the published documents but were published in abstract form.

Allocation concealment was not reported in the three published trial this is indicative of significant bias but in this review, we clarified allocation and concealment from the drug sponsors.

The protocols of the three trials were identical in the methods of titration and length of follow up. Patients were homogenous but some minor differences were seen in race. Despite similarities in the trials, we found differences in the individual adverse events. Five adverse events were reported in all three trials; these include diplopia, dizziness, headache, nausea and vomiting.

Ataxia was reported in Ben-Menachem but not reported in the other trials. Coordination abnormal was reported in the other two trials (Halasz and Chung). One might wonder if these two outcomes are synonymous as they would be to an astute clinician. However, without a review of the coding methods used one should not synonymise these two adverse events.

Rash and peripheral oedema were reported in Chung et al only, the reason for this could be related to a higher dose of lacosamide causing these adverse events being reported here.

Serious adverse events were reported in all three trials however the risk of serious adverse events was greater in the lower dose trial (Halasz 2009) as compared to Chung and Ben-Menachem.

7.6 Why was this review important for this thesis of adverse events?

This review highlighted a number of issues for this thesis. Frist the heterogeneity of adverse events reported in three trials, which had nearly identical protocols but only differed in dose regiment and escalation. One would have expected that all three trials would be similar in the types of adverse events reported but this was not the case. To our surprise, is the effect sizes for serious adverse events were higher in the low dose study as compared to the other studies. Adverse events such as peripheral oedema, rash and tremor were reported in Chung et al but not in the lower dose trials. In another trial of lacosamide used in neuropathic pain, we find that tremor was reported in one patient taking 200mg of lacosamide, five patients taking 400mg and nine patients taking 600mg (Wymer et al 2009). Moreover, asthenia is, reported in Wymer et al but not in the epilepsy trials. There are three other trials that used lacosamide in neuropathic pain.

The next question is can the harms outcome from these other trials be used in meta-analyses if there are no significant differences in protocol?

7.7 CONCLUSION

The results demonstrate the efficacy and safety of lacosamide in reducing seizure frequency using the responder rate as the outcome measure. Two studies did not find the 200mg dose to be efficacious compared to placebo, but our meta-analysis showed a marginal superiority over placebo, which was statistically significant. This could imply that patients need not to be titrated up to a high dose for the treatment to work and this would minimise adverse events.

Concluding remarks

- This review of lacosamide is a useful model to study adverse events as we have three trials that were essentially the same but differed in dose strengths. One would therefore expect that confidence intervals of effect sizes would be small and may even yield significant results. Indeed, this was the case for the 200mg dose of lacosamide.
- The lower 200mg per day dose of lacosamide can be considered to be of marginal benefit in patients with focal epilepsy.
- Lacosamide is effective at the 400mg and 600mg per day dose.
- This review of lacosamide is also unique in that the first two trials of lacosamide had failed to acquire a drug licence for UCB due to a nuisance placebo treatments effect. We therefore have three large trials of lacosamide for inclusion here. Effect sizes were relatively larger when harms were meta-analysed and this too could be a consequence of the placebo treatments effect.
- In this review four other randomised controlled trials of lacosamide that were similar in design to the epilepsy trials were mentioned. The next chapter explores harms in these four neuropathy trials.

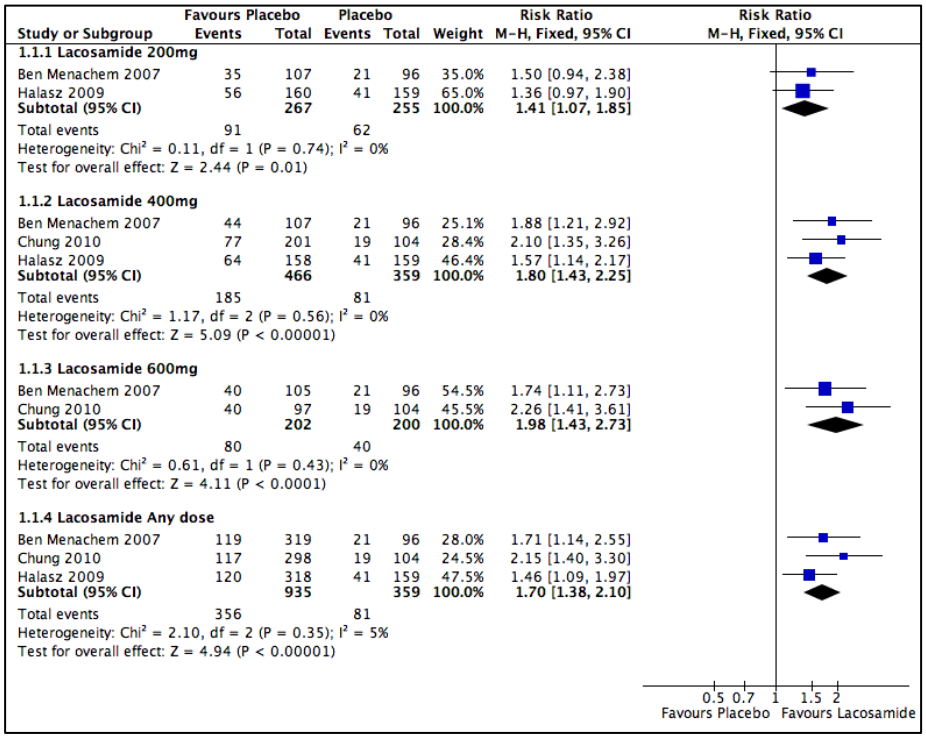

Figure 54 Outcome: Proportion of patients with greater than or equal to 50% reduction in seizure frequency

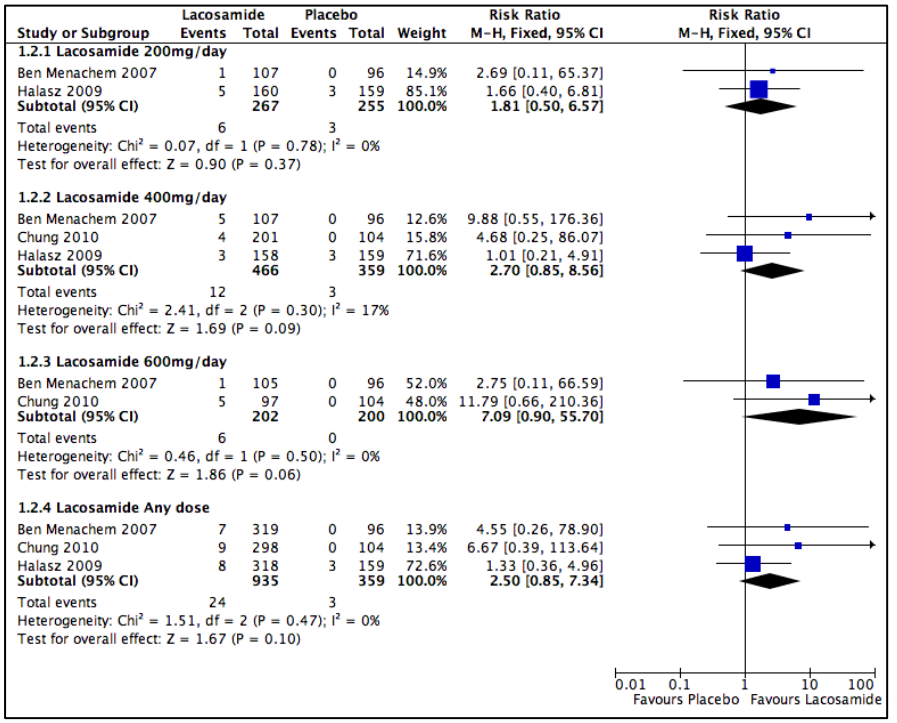

Figure 55 Outcome: Proportion of patients who become seizure free during the maintenance period.

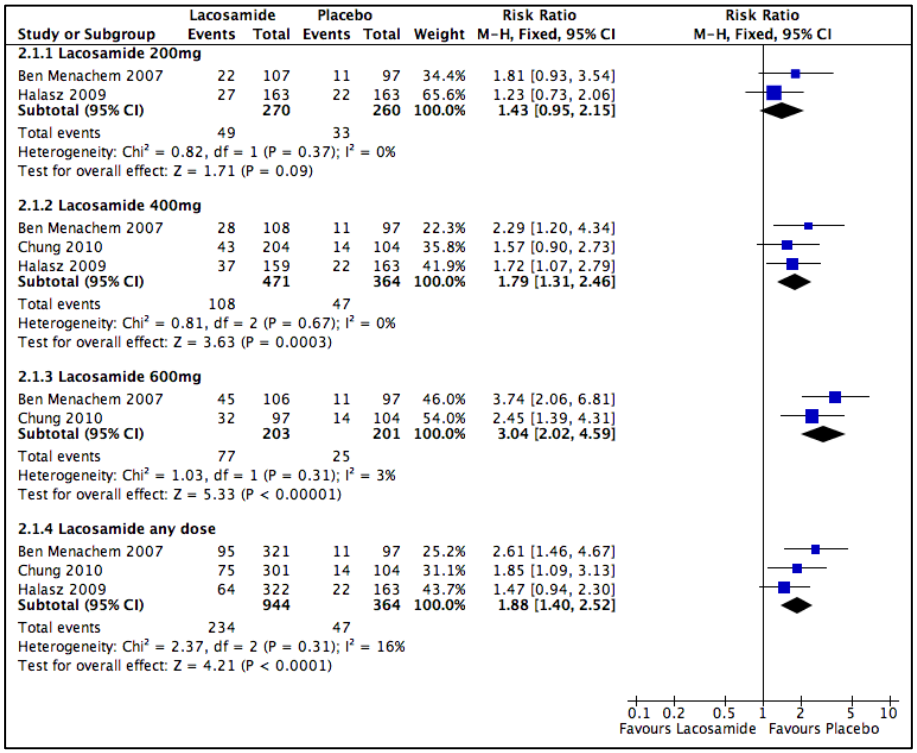

Figure 56 Outcome: Proportion of patients withdrawing due to adverse events

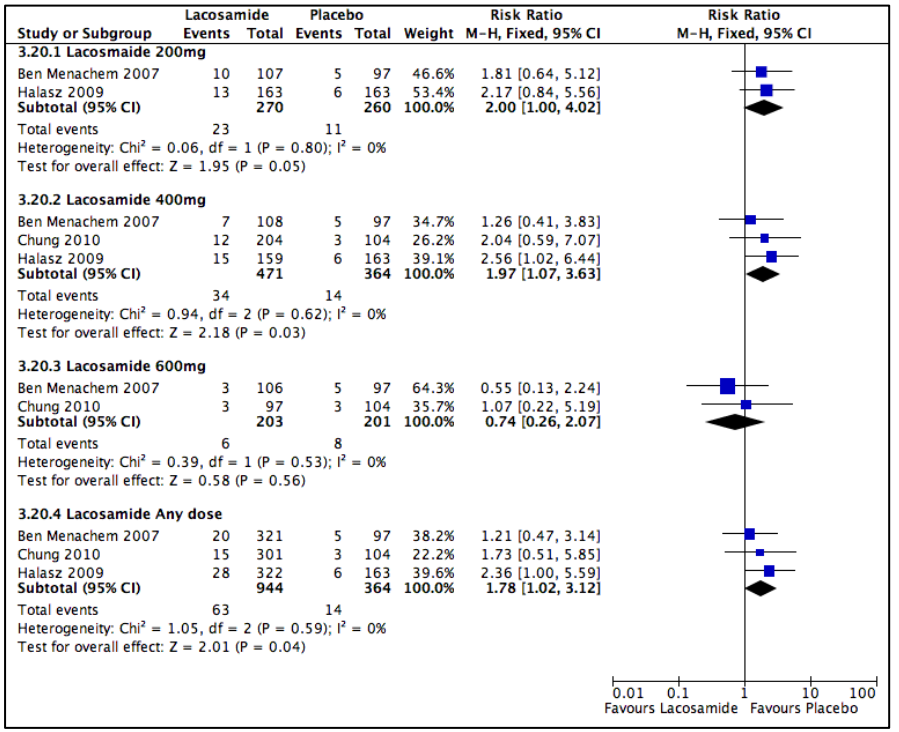

Figure 57 Outcome: Proportion of patients with serious adverse events

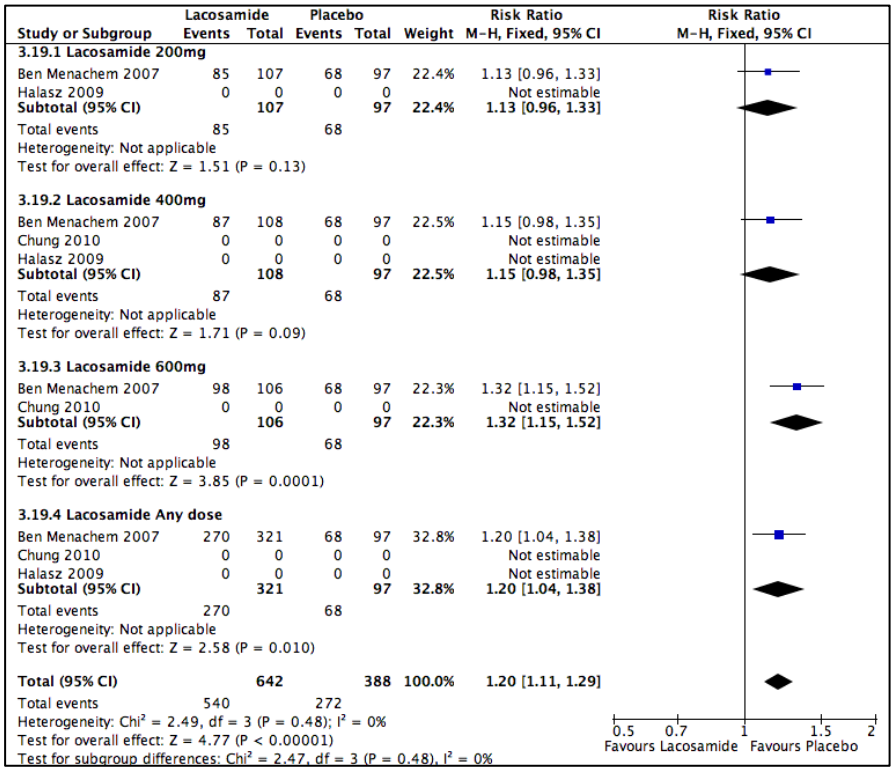

Figure 58 Outcome: Proportion of patients with Any Adverse Event

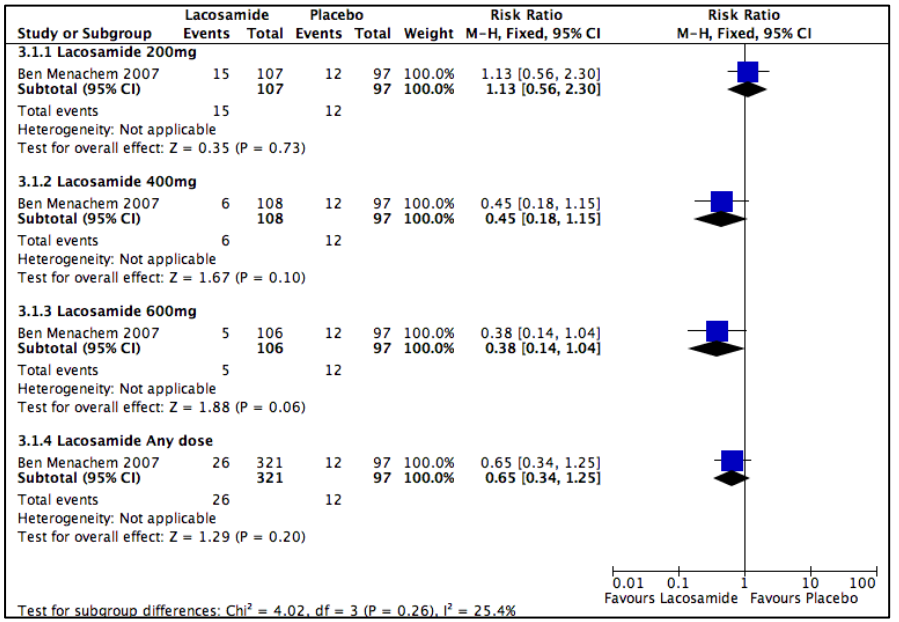

Figure 59 Outcome: Proportion of patients with Accidental injury not otherwise specified

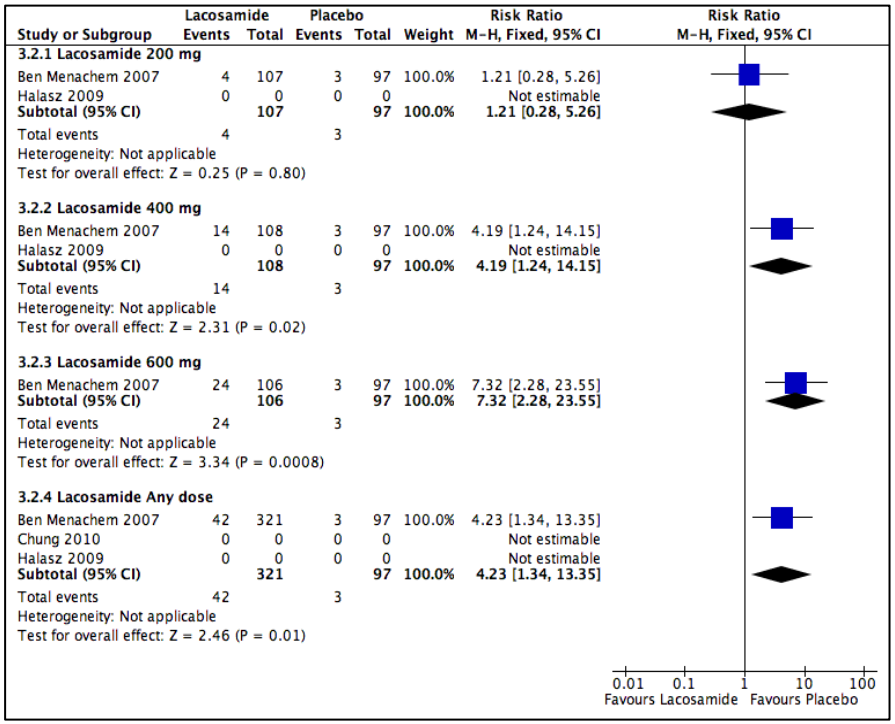

Figure 60 Outcome: Proportion of patients with Ataxia

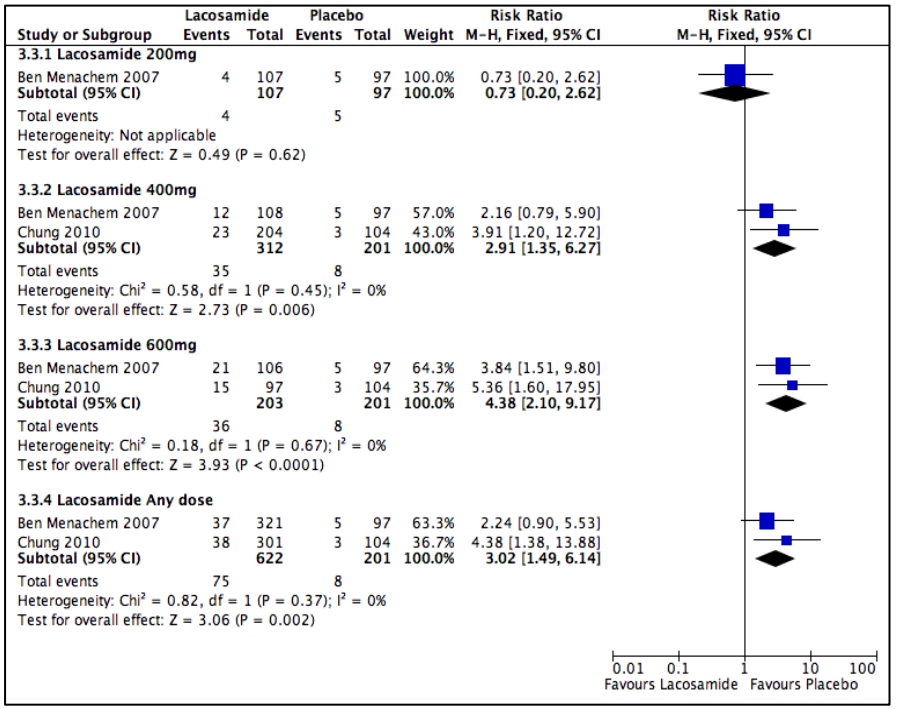

Figure 61 Outcome: Proportion of patients with Blurred Vision

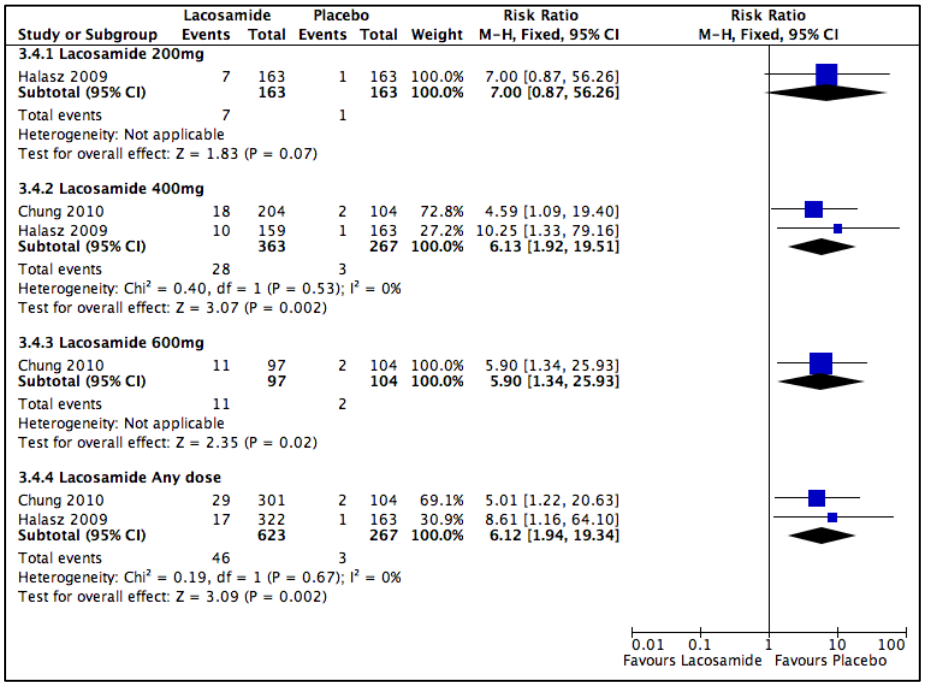

Figure 62 Outcome: Proportion of patients with Coordination Abnormal

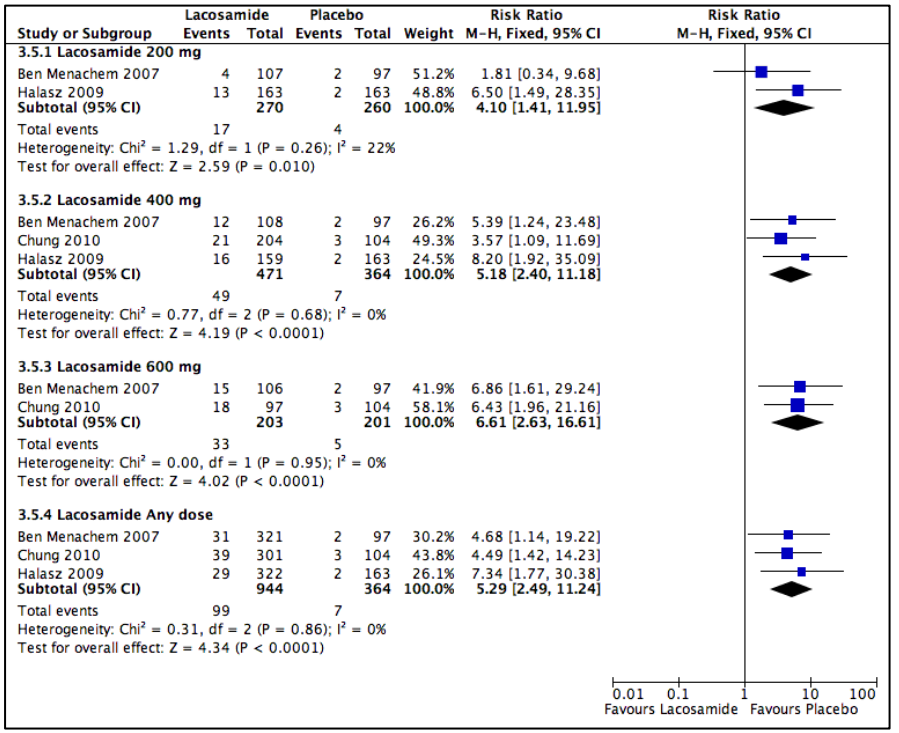

Figure 63 Outcome: Proportion of patients with Diplopia

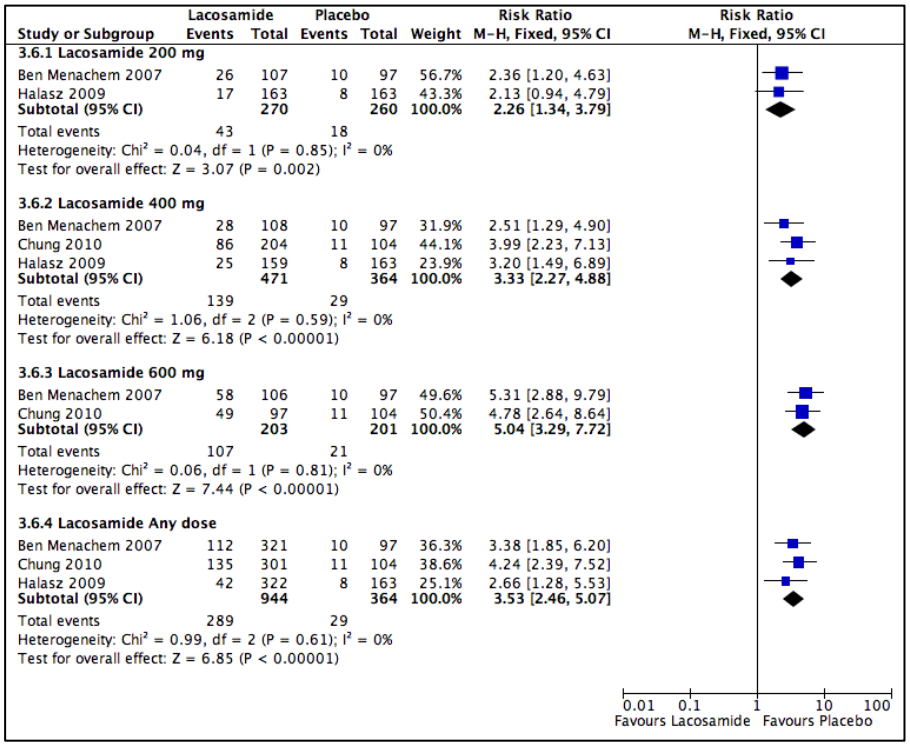

Figure 64 Outcome: Proportion of patients with Dizziness

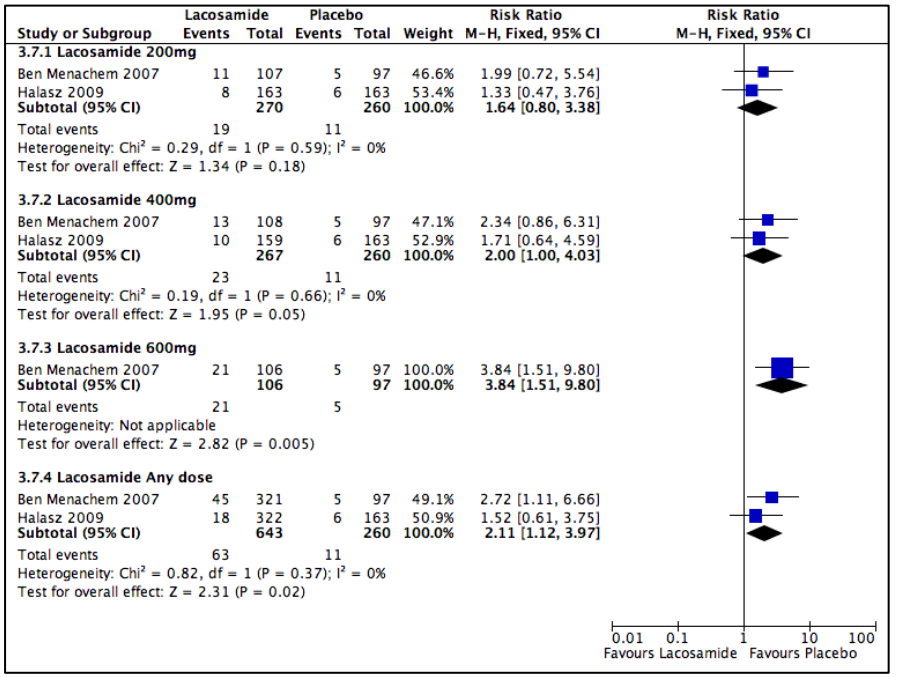

Figure 65 Outcome: Proportion of patients with Fatigue

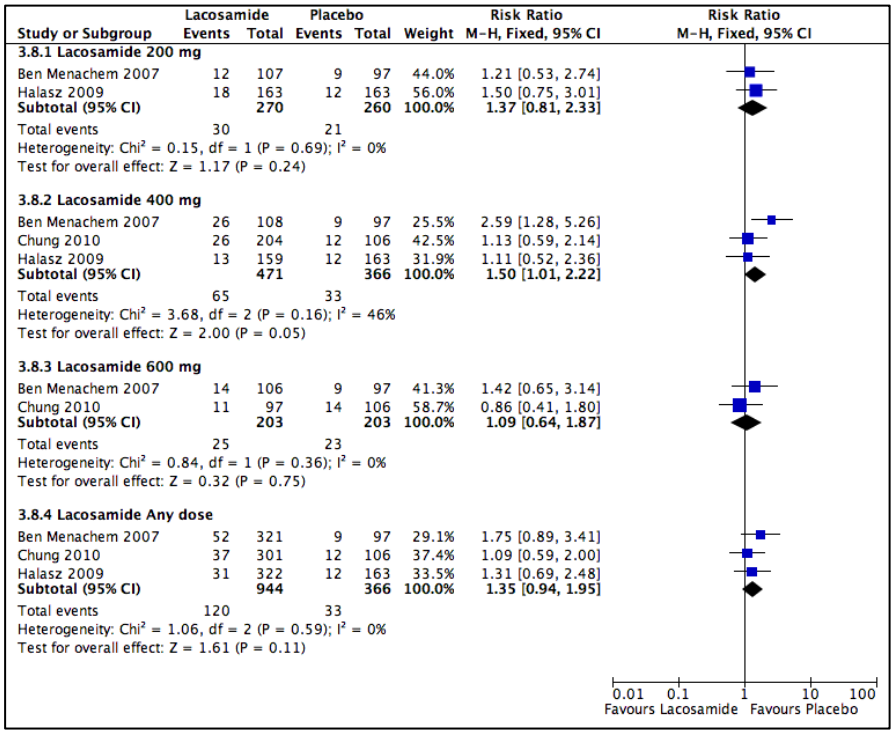

Figure 66 Outcome: Proportion of patients with Headache

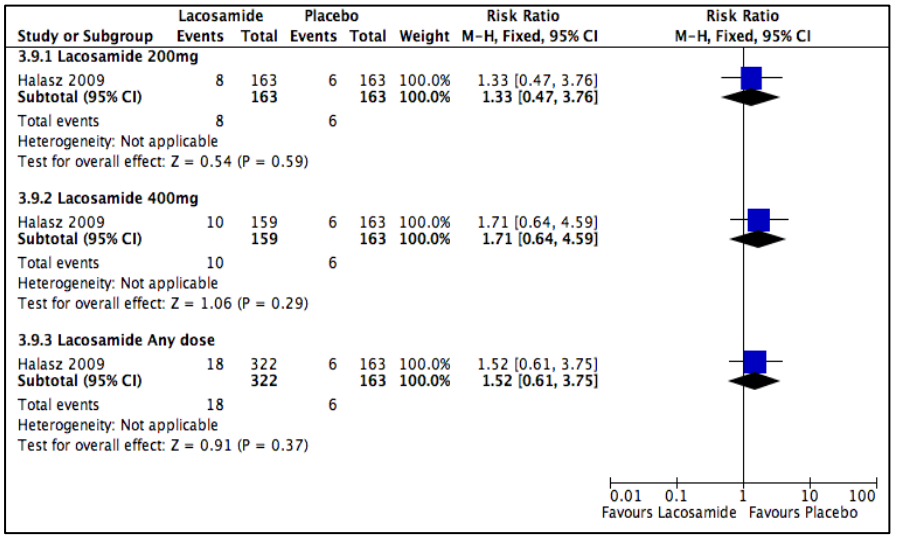

Figure 67 Outcome: Proportion of patients with Nasopharyngitis

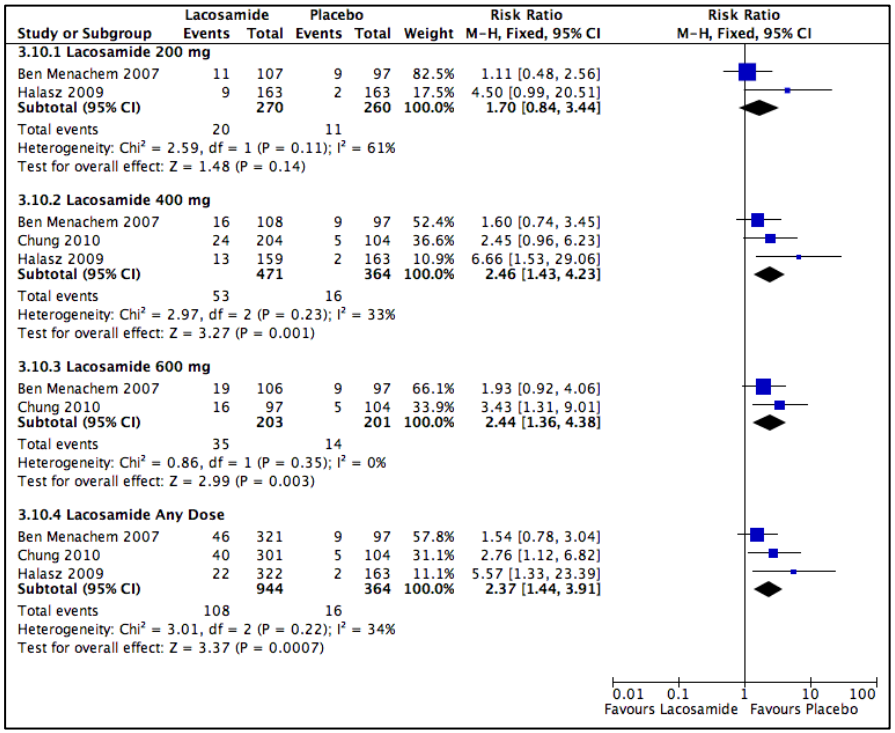

Figure 68 Outcome: Proportion of patients with Nausea

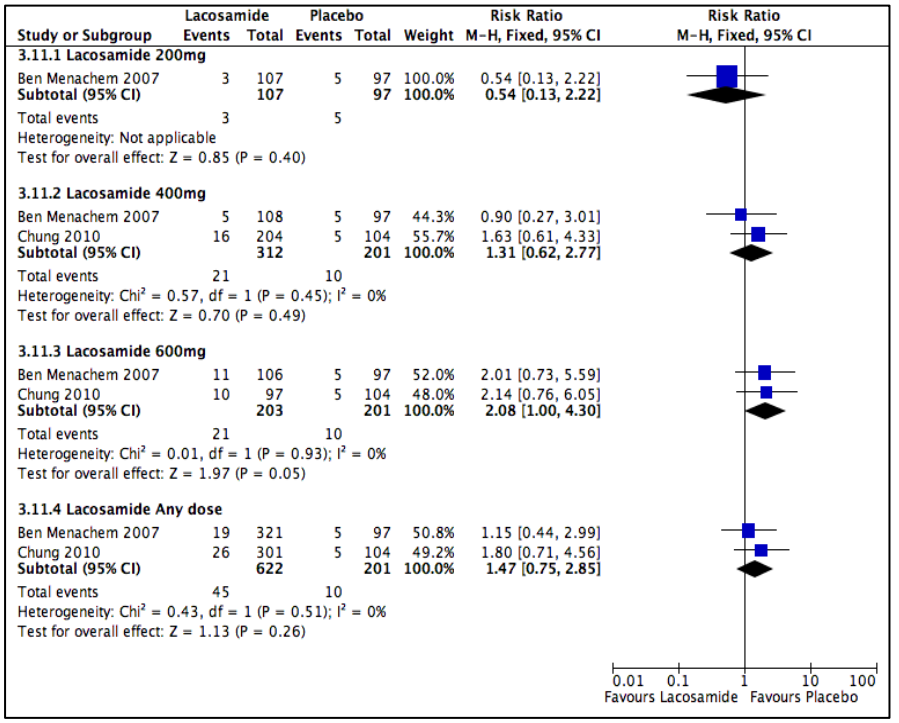

Figure 69 Outcome: Proportion of patients with Nystagmus

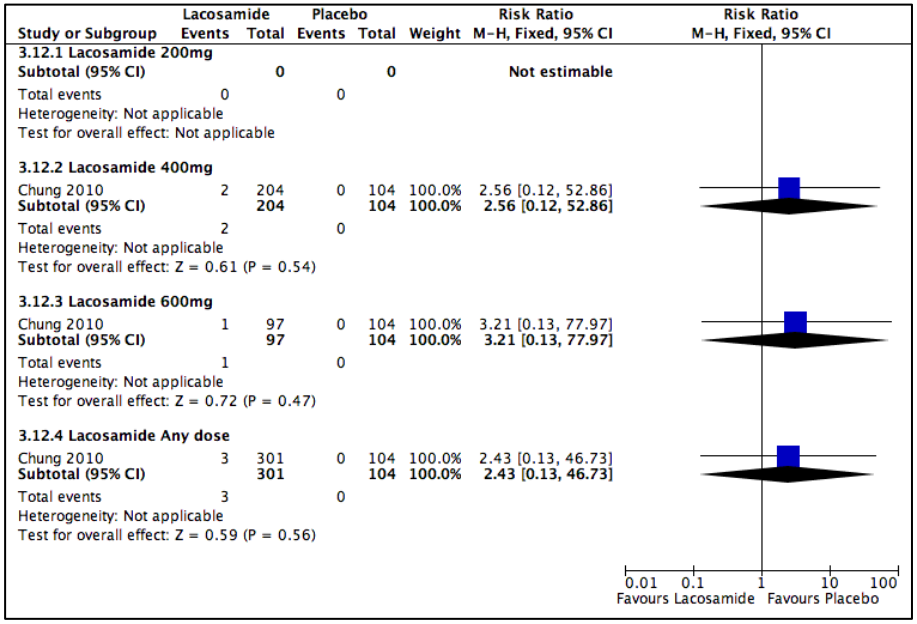

Figure 70 Outcome: Proportion of patients with Peripheral Oedema

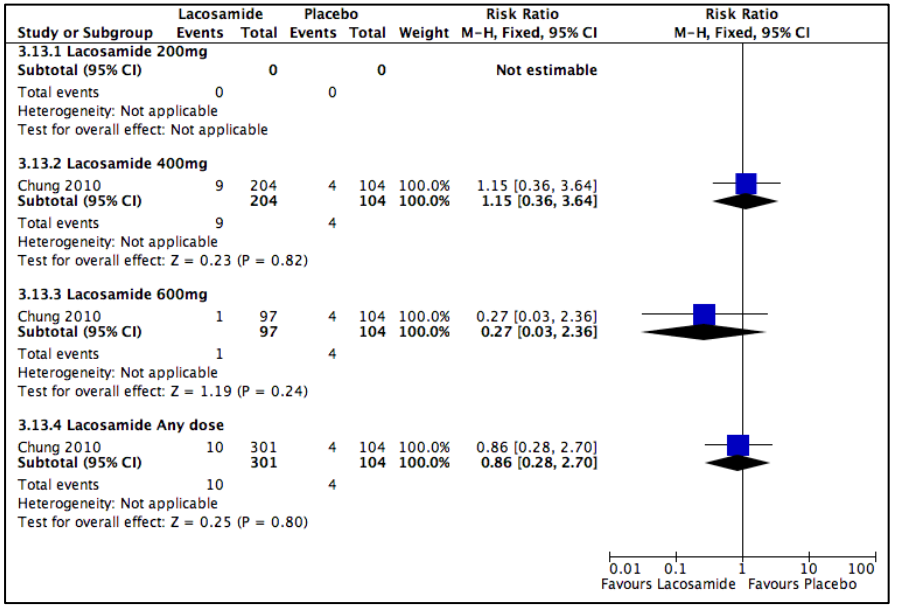

Figure 71 Outcome: Proportion of patients with Rash

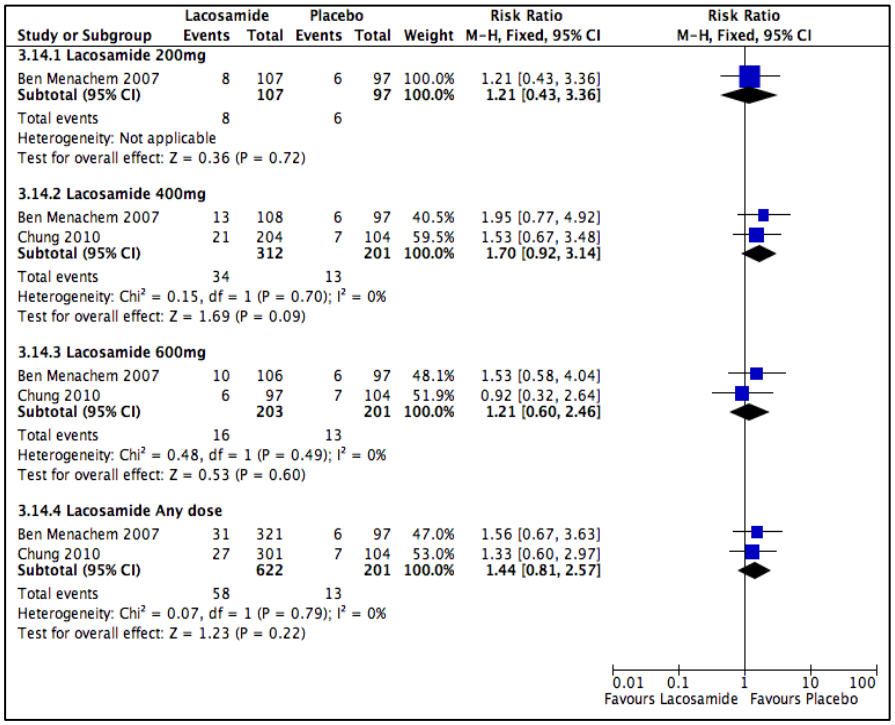

Figure 72 Outcome: Proportion of patients with Somnolence

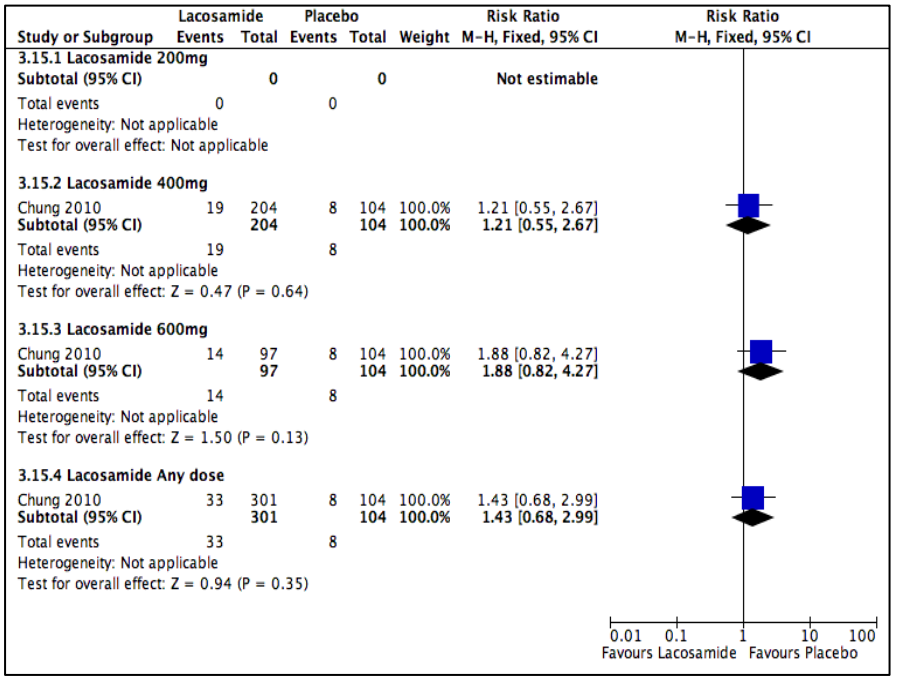

Figure 73 Outcome: Proportion of patients with Tremor

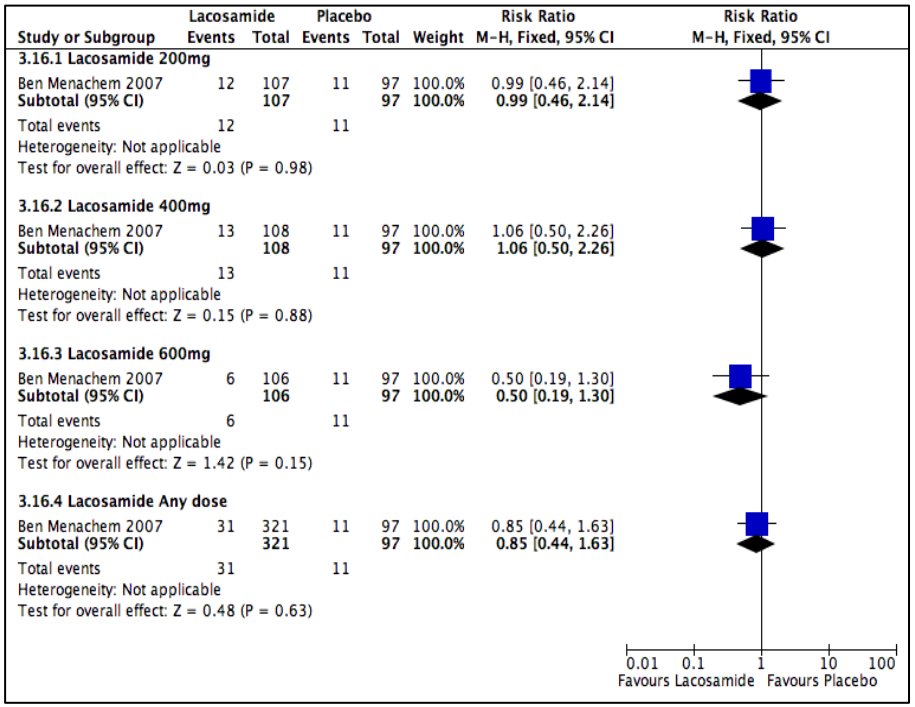

Figure 74 Outcome: Proportion of patients with URTI

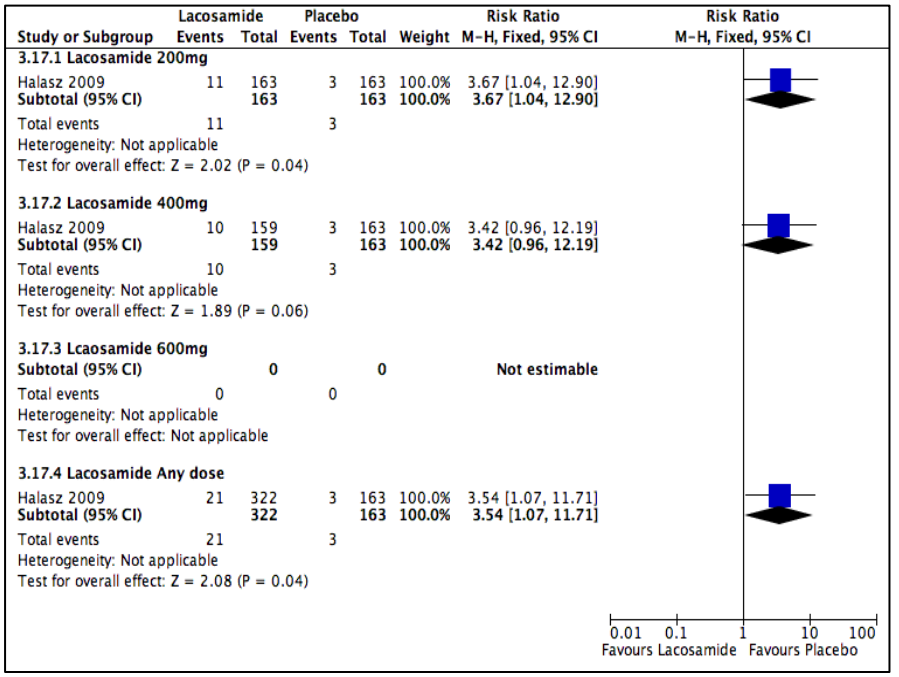

Figure 75 Outcome: Proportion of patients with Vertigo

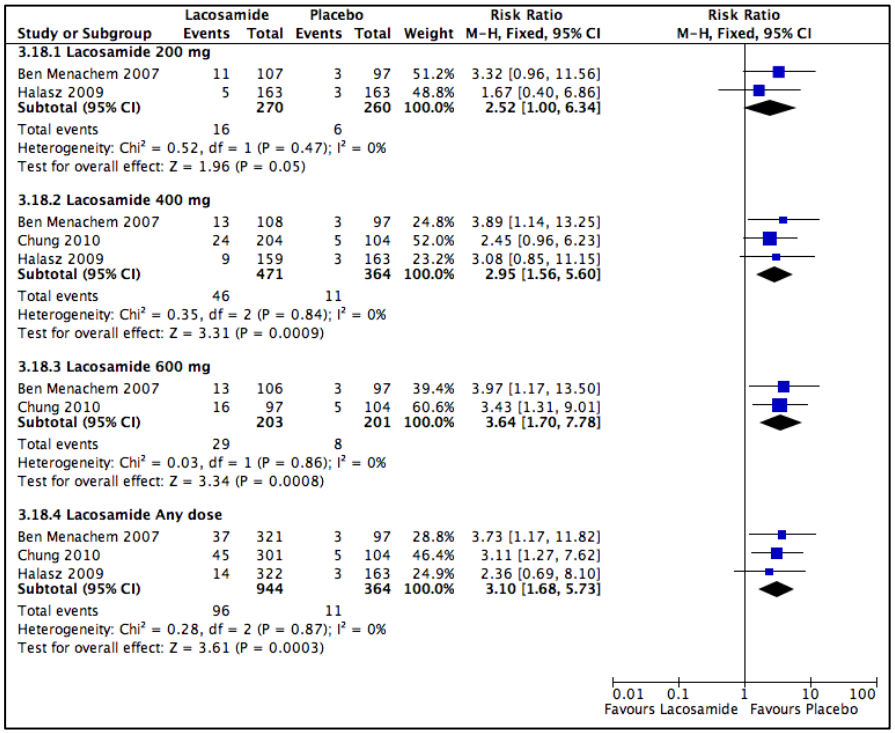

Figure 76 Outcome: Proportion of patients with Vomiting

Chapter 8

Adverse Events across indications: The Lacosamide example

8.1 Introduction

The previous chapters established that harms reporting is poor in RCTs and using lacosamide as an example we explored harms in systematic reviews. We also learnt that poor reporting is heterogeneous and this affects some aspect of harms reporting more than others. Furthermore, items in the methods section are reported the poorest as opposed to the results and discussion sections. This therefore makes the ascertaining of the risk of bias harder for a reviewer.

Antiepileptic drugs are used primarily to treat patients with epilepsy. These drugs can be used in other indications either as a licensed or as an off-license indication. These areas would include headache syndromes like cluster headache, migraine, SUNCT (short-lasting unilateral neuralgiform headache and conjunctival injection and tearing) and various painful peripheral neuropathies conditions like diabetic neuropathy and CIDP (chronic inflammatory demyelinating polyneuropathy). It would be likely that other trials of AEDs in indications other than epilepsy may exist and a drug company to obtain a licence may conduct these or they may be independent from industry as an exploratory trial.

Writing a systematic review is a structured process with the selection of outcomes and analysis of outcomes followed by an evaluation of the risk of bias. Most systematic reviews and meta-analyses include placebo-controlled trials. These trials are commonly funded by industry to obtain a license. Once a license is obtained, it is unlikely there will be another placebo-controlled trial in the same area but it is conceivable there may be placebo-controlled trials in other indications. These additional trials may be useful for improving harms data in systematic reviews.

Here I discuss how trials of lacosamide from other indications improve adverse events reporting.

8.2 Clinical trials of lacosamide: the other studies

8.2.1 Other indications for lacosamide

The use of lacosamide in partial epilepsy has now become common practice. When searching for studies of lacosamide in partial epilepsy; three placebo controlled trials of lacosamide for partial epilepsy were found. It was noted that there were other trials of lacosamide in the treatment of neuropathic pain. The idea that lacosamide can be used for neuropathic pain stemmed from experimental data, these showed that lacosamide reduced painful symptoms in rat models of diabetes (Beyreuther et al 2007). Following this there have been four trials in patients with painful diabetic neuropathy (Rauck et al 2007) (Shaibani et al 2009) (Wymer et al 2009) (Ziegler et al 2010). These trials did not meet regulatory approval for clinical use in neuropathy patients.

8.3 Searches for clinical trials

Using the search strategy of lacosamide in partial epilepsy. Searches were made in MEDLINE via the PubMed interface, the Cochrane database and OVID databases. Four trials of lacosamide in neuropathy were found. Description of inclusion and exclusion criteria is addressed in the next section. A diagram of the search results is displayed in fig 77 page 219. Searches revealed four studies of lacosamide in painful diabetic neuropathy (PDN) and three studies in Lacosamide in partial epilepsy. One study of intravenous lacosamide was excluded.

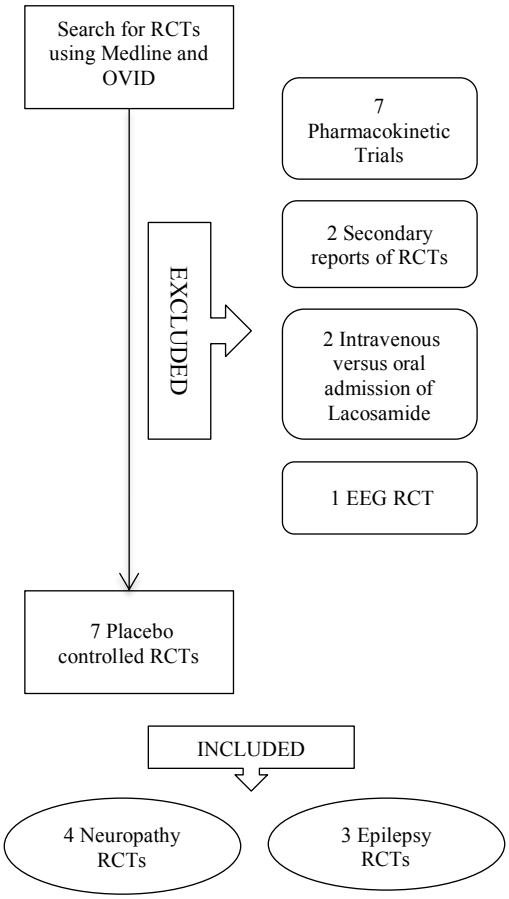

Figure 77 Flow diagram of included and excluded lacosamide studies

8.4 Inclusion and Exclusion criteria

Included trials were those of lacosamide in patients with painful neuropathy Trials needed to have a comparator arm which should be placebo. Trials have to be conducted on human subjects. Observational studies and trials not in English were excluded. A list of inclusion and exclusion criteria is shown below.

Included:

1. Randomised trials
2. Double blinded
3. Placebo controlled
4. Lacosamide studies

Excluded:

1. Observational studies
2. Trials not in English

8.5 Summary of clinical trials of painful diabetic neuropathy and partial epilepsy

8.5.1 Description of studies

All four trials used similar doses of lacosamide and all participants were with patients with painful diabetic neuropathy (PDN). The comparator group in seven trials was placebo. The primary outcomes were a change in pain score of a greater than 2-point reduction of on numerical rating scales. The patients' global impression of change (PGIC) is a generic validated tool to monitor a change in any patient related outcome (Hurst & Bolton 2004). The tables below describe the trials briefly. In addition, trials used in epilepsy are shown below although details of these trials are in chapter seven.

One can see from tables 46 and 47, that in all seven trials, lacosamide doses were similar; titration rates are similar across all seven trials. The titration period was 6 weeks in all seven trials. Maintenance phase for all six trials was the same. Therefore, there is no difference between these studies in terms of their methodological differences. Hence, as far as harms outcomes are concerned, these seven trials could undergo meta-analysis.

Trial	Patients	Primary outcome	Dose of Active interventio n	Compa rator	Harms outcomes	Titration	Phase Duration
Rauck 2007	Patients with PDN	Change in pain score & PGIC	Lacosamide 400mg	Placebo	Adverse events & withdrawals	100mg/day/ week plus back titration from 400mg to 300mg	6 wk Titration 4wk Maintenance
Shaibani 2009	Patients with PDN	Change in pain score & PGIC	Lacosamide 200mg, 400mg and 600mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 12 wk Maintenance
Wymer 2009	Patients with PDN	Change in pain score & PGIC	Lacosamide 200mg, 400mg and 600mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 12 wk Maintenance
Ziegler 2010	Patients with PDN	Change in pain score & PGIC	Lacosamide 400mg and 600mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 12 wk Maintenance

Table 46 Description of lacosamide trials used in neuropathy: peripheral diabetic neuropathy (PDN)

Trial	Patients	Primary outcome	Dose of Active intervention	Comparator	Harms outcomes	Titration	Phase Duration
Ben-Menachchem 2007	Patients with focal epilepsy	Proportion of patients with >50% reduction in seizures	Lacosamide 200mg 400mg and 600mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 4wk Maintenance
Halasz 2009	Patients with focal epilepsy	Proportion of patients with >50% reduction in seizures	Lacosamide 200mg, 400mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 4wk Maintenance
Chung 2010	Patients with focal epilepsy	Proportion of patients with >50% reduction in seizures	Lacosamide 400mg and 600mg	Placebo	Adverse events & withdrawals	100mg/day/ week	6 wk Titration 4wk Maintenance

Table 47 Description of lacosamide trials used in epilepsy.

8.5.2 Outcome measures in painful diabetic neuropathy trials

The primary outcomes in trials for neuropathy and epilepsy are different; seizure outcomes are not the same as pain outcomes. However, adverse events could be summated in meta-analyses. It is further noted that all trials used a similar weekly titration scheme. Patients were allowed back titration is some arms (Chung et al 2010 with the 600mg dose) and Wymer et al compared two 400mg doses one with a 6-week titration and one with a 4-week titration but both arms were at 100mg/day/week increments (2009). With similar titration schemes in these studies, one can assume that withdrawals due to harms can be compared.

8.6 Hypothesis

Given that the drug doses, titration schedules and duration of trial is similar in the included studies, one would hypothesize that any differences between outcomes measures in individual trials is due to clinical differences.

The null hypothesis is that there will not be significant statistical heterogeneity and therefore these harms data can be combined in a meta-analysis. Where the null hypothesis is defined as:

H_0 = Chi sq with n degrees of freedom has a p value > 0.05

Or

H_0 = Tau squared is low with p > 0.05

Some harms outcomes like headache, nystagmus and somnolence were not significantly different compared to placebo in the lacosamide trials. An important question is if data from neuropathy trials may change the direction of the effect in meta-analyse or yield a more precise summary estimate.

Also, we took a more pragmatic approach to see if harms across indications could give us better precision in effect sizes

8.7 Methods

8.7.1 **Results from epilepsy trials**

It is important to note that headache and somnolence were not significant compared to placebo in trials of epilepsy when these outcomes were meta-analysed. The relative risk of headache in lacosamide for any dose was 1.35 with 95% confidence interval of 0.83 to 2.19 including unity. The relative risk of somnolence was 1.44 with 95% CI of 0.81 to 2.57 including unity. It would be important to see if these outcomes became statistically significant when data from neuropathy trials were pooled.

8.7.2 How the data was extracted.

Harms data was extracted from selected trials, given that this was not a formal Cochrane review. Items of data that were collected include; the proportion of patients with Lacosamide or placebo that experienced adverse events. The proportion of patients that have any adverse events and the proportion of patient withdrawn due to adverse events.

8.7.3 Data analysis

In the previous chapter a fixed effect model was used. However, when we meta-analyse trials from other indications, this would not be appropriate and therefore the random effects model will be used. This may have an impact on the precision of summary estimates by producing estimates with a wider confidence interval and therefore less precise estimates

Summary measures of the risk of adverse events were calculated using the Mantel-Henszel method. Using measures of heterogeneity, decisions were made if harms from across indications can be used. These measures include: Chi squared statistic, I^2 and tau squared statistics. Data was analysed using RevMan 5.0. Forest plots displaying summary measures and statistics of heterogeneity were used to make decisions if the null hypothesis is true or false.

Details of the rationale and theory of meta-analyses have been described in preceding chapters.

8.8 Results

To decide which adverse events are evaluable, only those adverse events, which are reported in at least one epilepsy trial and one neuropathy trial, were included. The table below (table 48) shows those that are for inclusion. In addition to adverse events, , withdrawals due to adverse events and the total number of adverse events were also analysed.

Thirty-six discreet adverse events were reported across all trials. Out of these 19 were reported in the neuropathy trials. Twelve adverse events are reported in both indications but not necessarily in all trials. Six adverse events were reported in epilepsy trials and not neuropathy trials.

Adverse events that were reported only in neuropathy trials include: Abdominal pain; anxiety; asthenia; back pain; balance disorder; constipation; diarrhoea; erythematous

rash; flatulence; hypoesthesia; hypoglycaemia, influenza; memory impairment; myalgia; nervousness; paraesthesia; pruritus; sinusitis and tachycardia.

Adverse events that were reported in epilepsy trials only include; accidental injury; ataxia; coordination abnormal; vision abnormal and nystagmus.

There are twelve harms outcomes that are reported in both indications. These adverse events include; Diplopia; dizziness; fatigue; headache; nasopharyngitis; nausea; somnolence; tremor; URTI; vertigo; vision blurred and vomiting. Also evaluated were 'any adverse event' and withdrawals due to adverse events.

The table below (table 48 page 225) shows a list of adverse events reported in all seven lacosamide trials. Outcomes that are reported in at least one epilepsy and at least one neuropathy trials are highlighted in red. These outcomes are therefore included in analyses.

Figures 78 to 89 on pages 226 to 237 display the forest plots and statistical tests of heterogeneity for outcome analysed.

Table 48 Harms outcomes reported in seven lacosamide trials

Harms outcome	Ben-Menachem 2007	Chung 2010	Halasz2007	Shaibani 2009	Rauck 2007	Wymer 2009	Ziegler 2010
Abdominal pain					✓		
Accident NOS	✓						
Anxiety					✓		
Asthenia						✓	
Ataxia	✓						
Back pain				✓	✓	✓	
Balance disorder				✓		✓	
Constipation					✓		
Coordination abnormal		✓	✓				
Diarrhoea				✓	✓	✓	
Diplopia	✓	✓	✓			✓	
Dizziness	✓	✓	✓	✓	✓	✓	✓
Erythematous rash					✓		
Fatigue	✓		✓	✓		✓	✓
Flatulence				✓			
Headache	✓	✓	✓	✓	✓	✓	✓
Hypoesthesia				✓			
Hypoglycaemia					✓		
Influenza						✓	
Memory impairment						✓	
Myalgia					✓		
Nasopharyngitis			✓			✓	
Nausea	✓	✓	✓	✓	✓	✓	✓
Nervousness					✓		
Nystagmus	✓	✓					
Paraesthesia					✓		
Pruritus				✓			
Sinusitis				✓			
Somnolence	✓	✓		✓	✓		
Tachycardia					✓		
Tremor		✓		✓	✓	✓	
URTI	✓				✓	✓	
Vertigo			✓	✓		✓	✓
Vision abnormal	✓						
Vision blurred		✓		✓			
Vomiting	✓	✓	✓	✓			✓

8.8.1 Any Adverse Event: Meta-analysis using the Random effects model

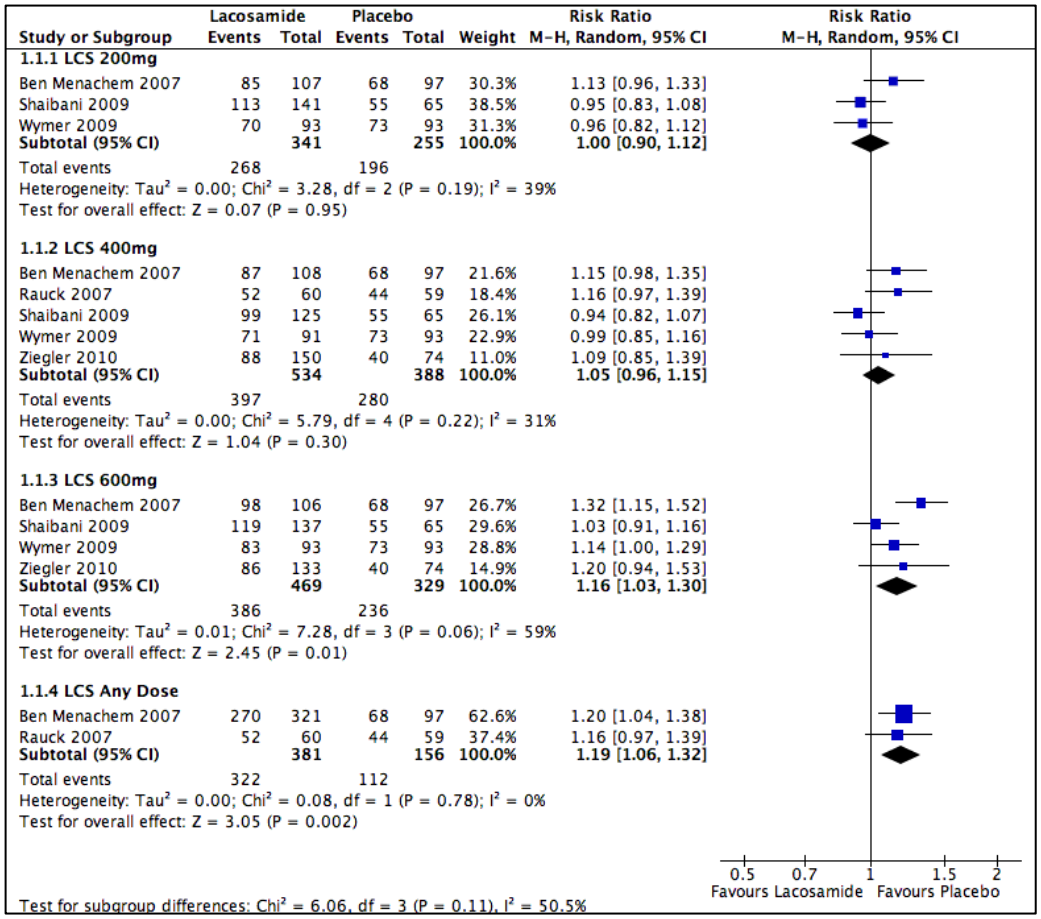

Figure 78 Proportion of patients with Any Adverse Event across indications

Any adverse event was reported in Ben-Menachem (2007) only and not the other three epilepsy trials. (Halasz 2009) (Chung 2010). Any adverse event was reported in three neuropathy trials (Rauck 2007, Shaibani 2009 and Wymer 2009). All four subgroups showed a Tau squared of 0.00 to 0.01 indicating no variance between studies. A quick view of the chi squared shows that the chi squares relative the degrees of freedom is not significantly different therefore the p-values are non-significant. Using both these methods one can conclude there is no significant heterogeneity. The effect sizes showed moderate variation and this was reflected in the value of I^2 proportions ranging from 39% to 59%.

Null hypothesis therefore is true but there is an increase in variance of summary measures when outcome any adverse event is meta-analysed.

8.8.2 **Dizziness: Meta-analysis using the Random effects model**

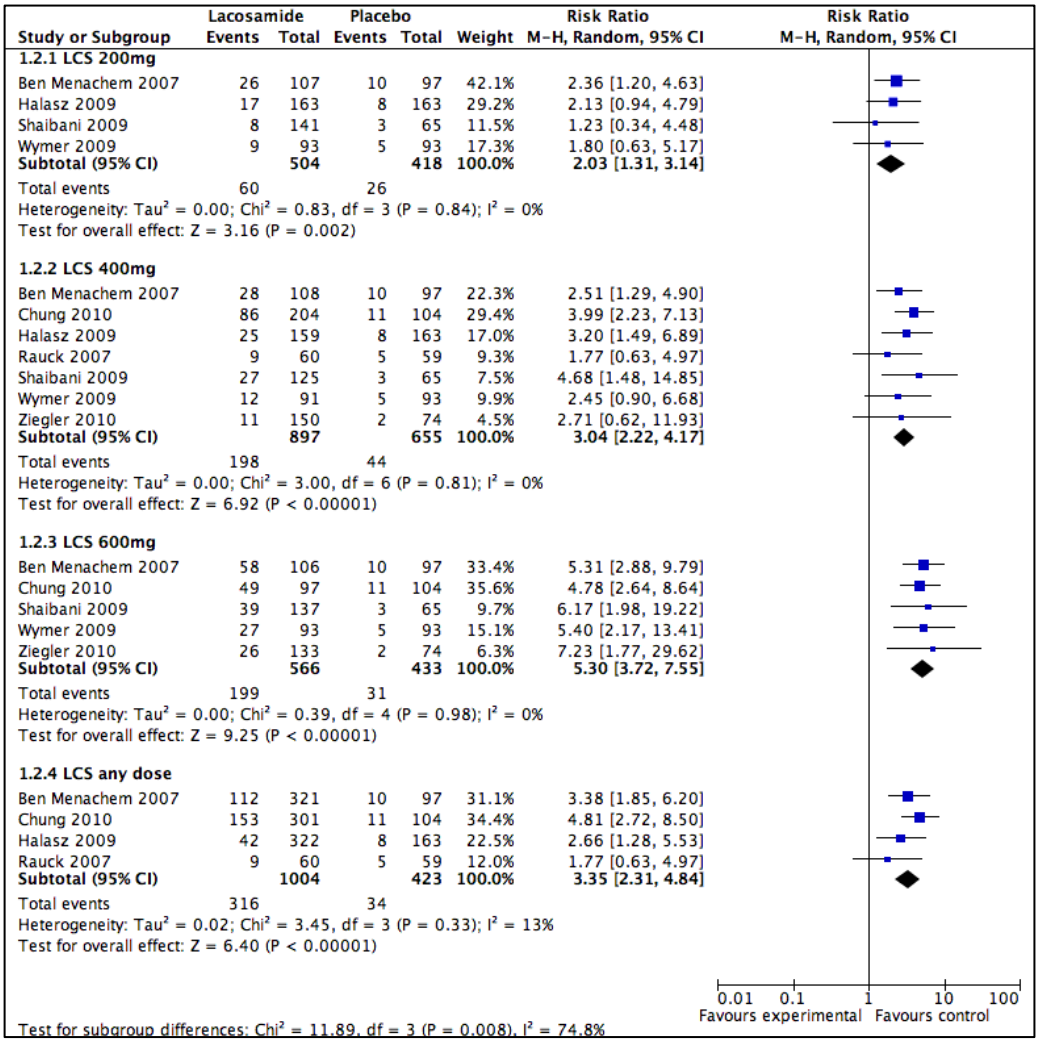

Figure 79 Proportion of patients with Dizziness across indications

For dizziness, all seven trials were included in the analysis. Tau squared statistics in the subgroups is between 0 and 0.02. This indicates there is no between study variance. The effect sizes across the studies do not vary significantly and therefore the I^2 proportions are low. P values for chi-squared statistic show no significant differences therefore one can conclude there is no statistical heterogeneity between trials.

Null hypothesis is true for this outcome.

8.8.3 Fatigue: Meta-analysis using the Random effects model

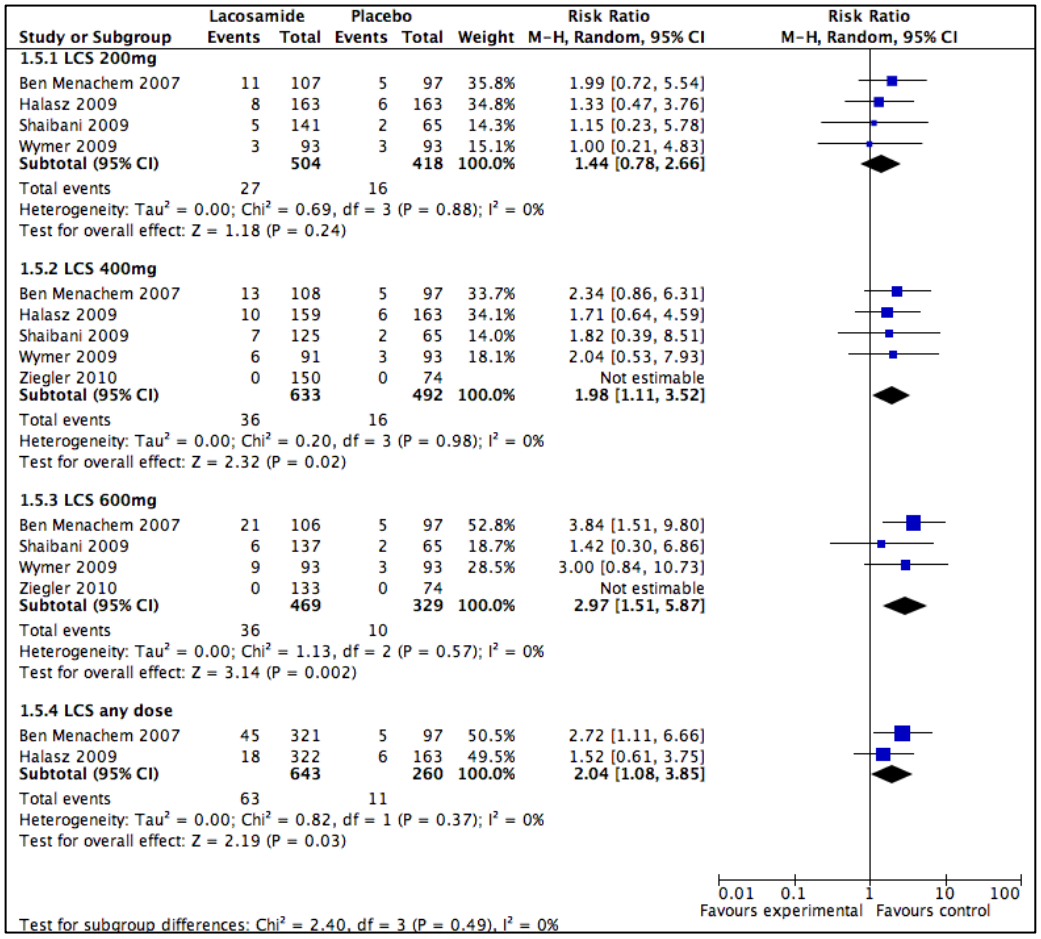

Figure 80 Proportion of patients with Fatigue across indications

For fatigue, two epilepsy trials (Ben-Menachem 2007 and Halasz 2009) were included and three neuropathy trials (Shaibani 2009, Wymer 2009 and Ziegler 2010). Tau squared across subgroups is low indicating no variance in between studies. I^2 proportions are low and chi squared statistic values are low and p values are non-significant. These indicate that outcome fatigue has no statistical heterogeneity between studies.

Null hypothesis is true for this outcome.

8.8.4 **Headache: Meta-analysis using the Random effects model**

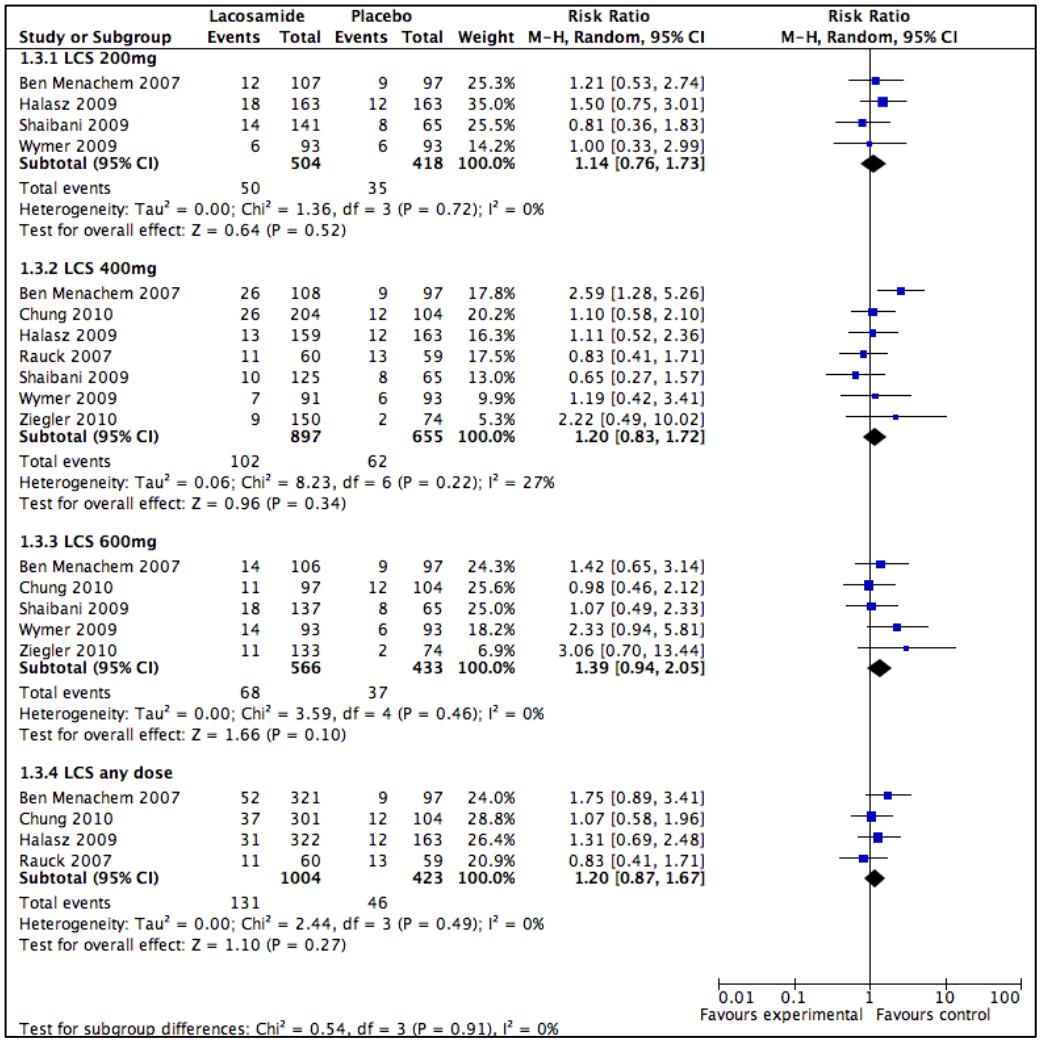

Figure 81 Proportion of patients with Headache across indications

For outcome headache, all seven studies were included. There was no between study variance as Tau squared statistic values ranged from 0 to 0.06. Some heterogeneity was seen in the effect sizes for the 400mg subgroup with an I^2 value of 27%. Chi squared values were low except for the 400mg dose with a Chi squared of 8.23 with 6 degrees of freedom. However, the p value was 0.22 indicating that the null hypothesis can be accepted as true and there was no evidence of statistical heterogeneity between indications for this outcome.

Null hypothesis is true for this outcome

8.8.5 Nasopharyngitis: Meta-analysis using the Random effects model

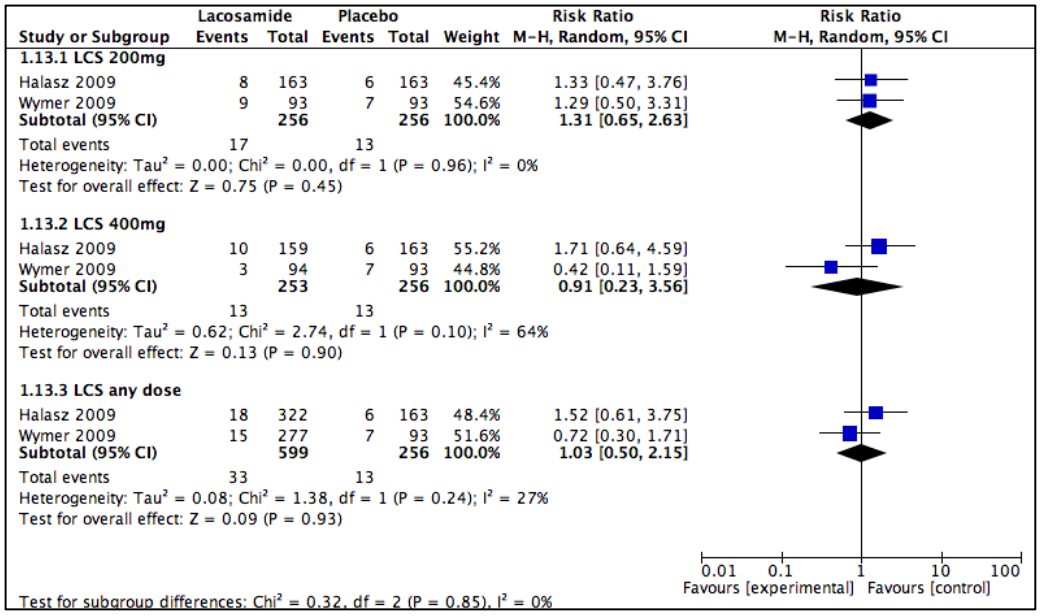

Figure 82 Proportion of patients with Nasopharyngitis across indications

For outcome nasopharyngitis, one epilepsy trial (Halasz 2009) and one neuropathy trial (Wymer 2009) was included. Both trials showed no significant difference in relative risks of nasopharyngitis compared to placebo. Calculated summary measures showed no significant difference compared to placebo for the three dose subgroups of 200mg, 400mg and any dose. Tau squared statistics showed no or low variance between studies for the 200mg and any dose but there was significant variance in the 400mg dose between studies with a corresponding I^2 value of 64% indicating significant statistical heterogeneity.

Therefore, one can conclude that trials across indications for this outcome cannot be meta-analysed.

Null hypothesis is not true for this outcome.

8.8.6 Nausea: Meta-analysis using the Random effects model

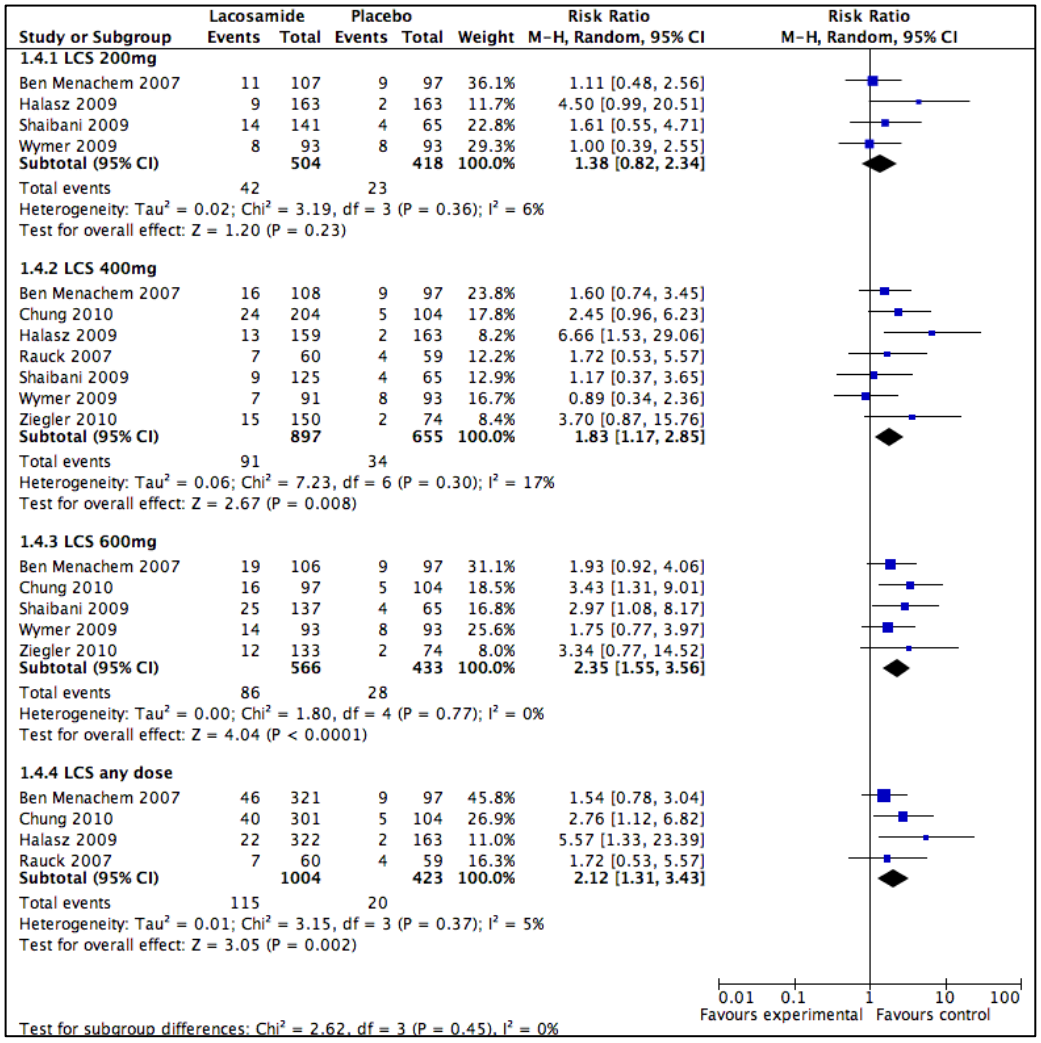

Figure 83 Proportion of patients with Nausea across indications

For outcome nausea, all seven trials were included. There was no variance between studies reflected by the low values of Tau squared. Heterogeneity was low reflected in low I^2 values and chi squared values were low. For the 400mg dose the chi squared was 7.23 with 6 degrees of freedom, hence the p value was 0.30 indicating the null hypothesis is true. Therefore, one can conclude that trials across indications can be used for this outcome.

Null hypothesis is true for this outcome.

8.8.7 Somnolence: Meta-analysis using the Random effects model

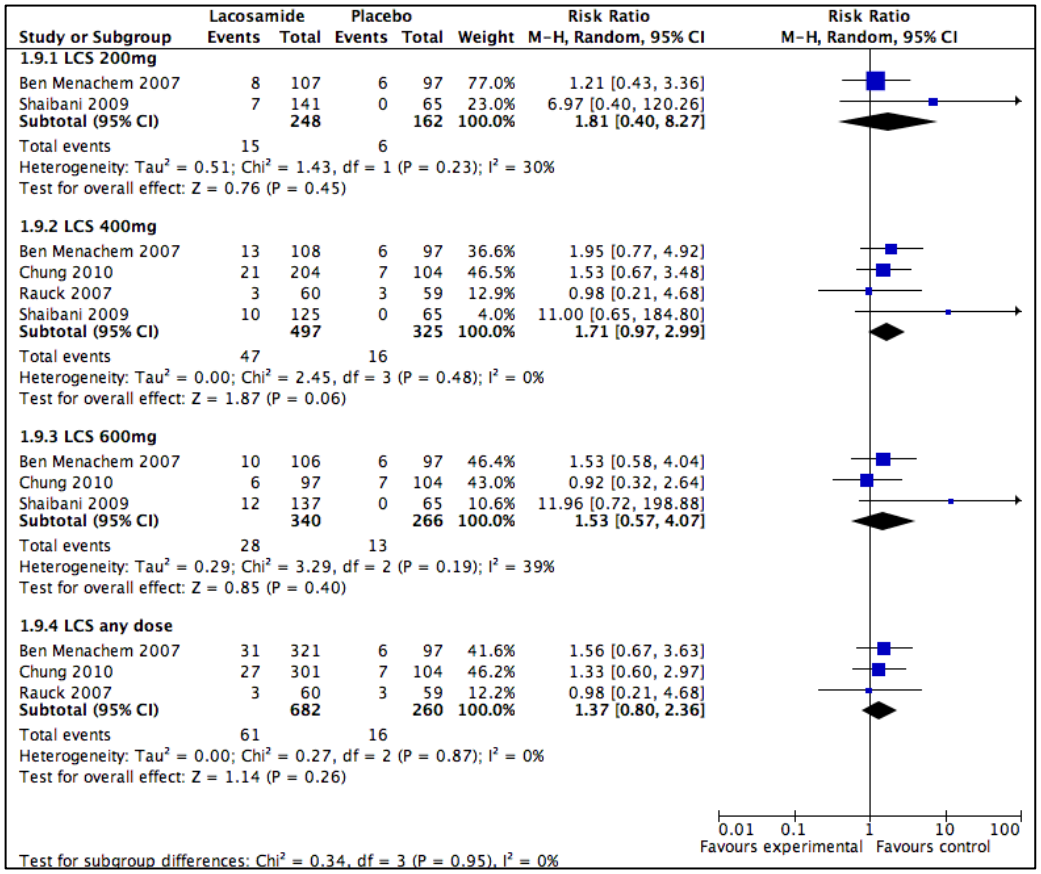

Figure 84 Proportion of patients with Somnolence across indications

For outcome somnolence two epilepsy trials (Ben-Menachem 2007 and Chung 2009) and two neuropathy trials (Shaibani 2009 and Rauck 2007) were included. The relative risk of somnolence from lacosamide in patients recruited into Shaibani (2009) was significantly greater compared to the other three trials. Statistical heterogeneity was present for only two subgroups; the 200mg and 600mg doses.

Tau squared showed some variance between studies largely due to variance between Shaibani (2009) and the other studies. The differences in somnolence to some extent could be due to chance. Moreover, the I^2 statistic suggested that about 60% of the variance could be due to chance alone and the remaining 39% is due to real differences.

Null hypothesis is true for this outcome.

8.8.8 Tremor: Meta-analysis using the Random effects model

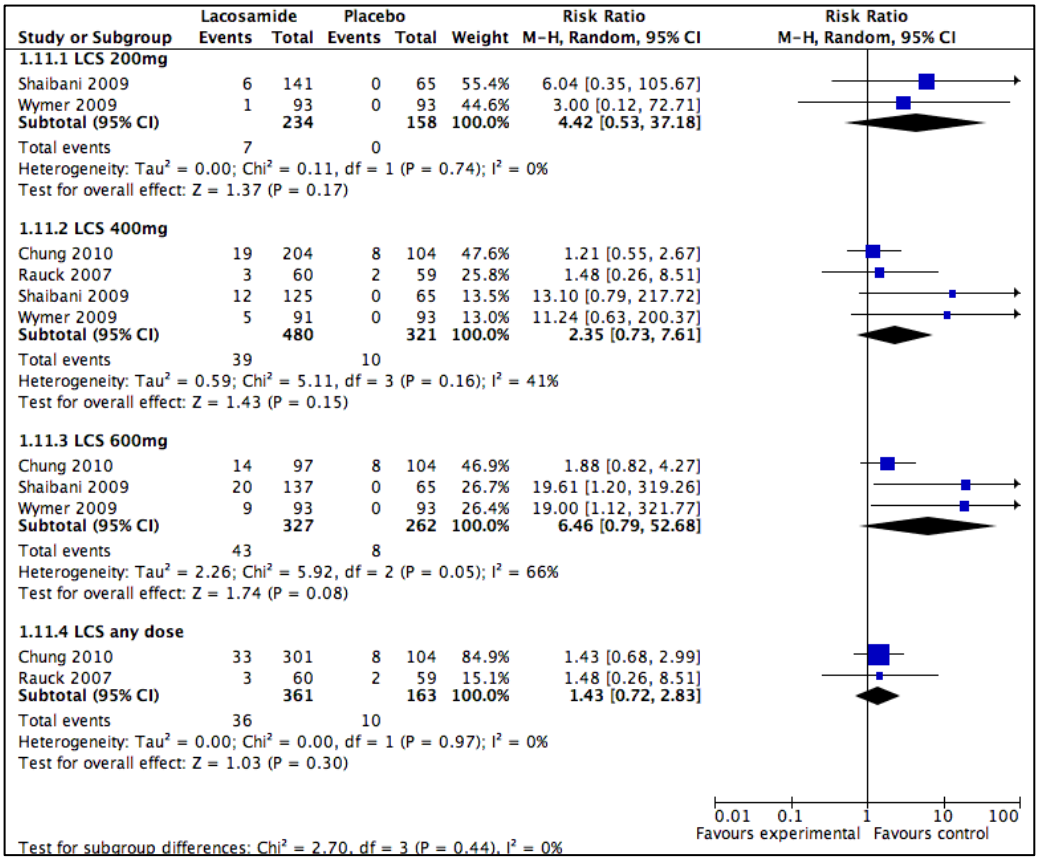

Figure 85 Proportion of patients with Tremor across indications

For outcome tremor, one epilepsy trial (Chung 2010) and three neuropathy trials (Rauck 2007, Shaibani 2009 and Wymer 2009) were included. The effect sizes for the neuropathy trials were significantly greater compared to the epilepsy trial. This was evident in the 400mg and 600mg subgroups. Tau squared in these two subgroups showed values of 0.59 and 2.26 indicating significant variability between studies. One can conclude that trials from neuropathy cannot be combined with epilepsy trials in a meta-analysis.

Null hypothesis is not true for this outcome.

8.8.9 Vertigo: Meta-analysis using the Random effects model

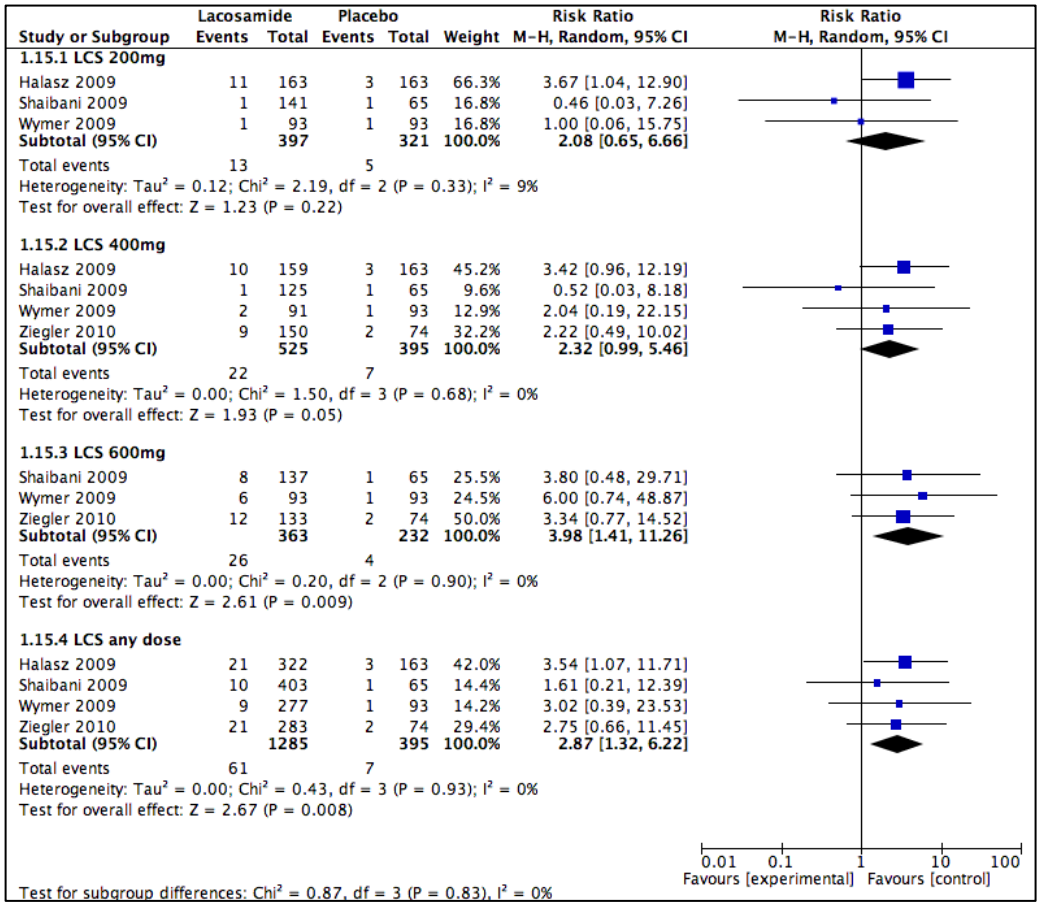

Figure 86 Proportion of patients with Vertigo across indications

For outcome vertigo, one epilepsy trial was included (Halasz 2009) and three neuropathy trials (Shaibani 2009, Wymer 2009 and Ziegler 2010). There was little variance between studies reflected in the low Tau squared values. There was no significant statistical heterogeneity reflected in the low I^2 values. The outcome vertigo can be used across indications for lacosamide.

Vertigo was not reported in Chung 2010 and Ben-Menachem (2007) in the 600mg dose.

Null hypothesis is true for this outcome

8.8.10 Vision Blurred: Meta-analysis using the Random effects model

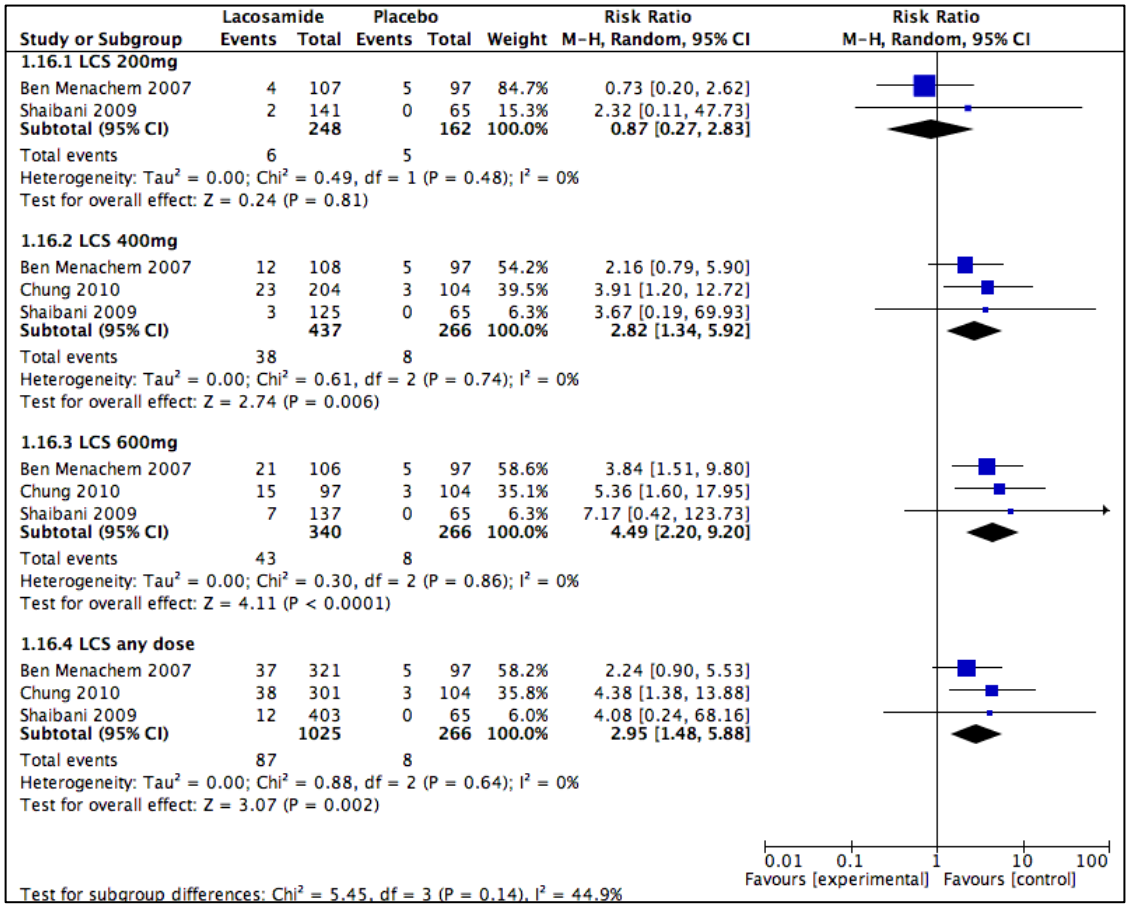

Figure 87 Proportion of patients with Vision Blurred

For the outcome vision blurred, two epilepsy trials (Chung 2010 and Ben-Menachem) and one neuropathy trial (Shaibani 2009) were included. There was little variance between studies reflected in the low Tau squared values. P-value for I^2 were non-significant indicating no heterogeneity. One can therefore conclude that vision blurred can be used across indications for lacosamide.

Null hypothesis is true for this outcome.

8.8.11 Vomiting: Meta-analysis using the Random effects model

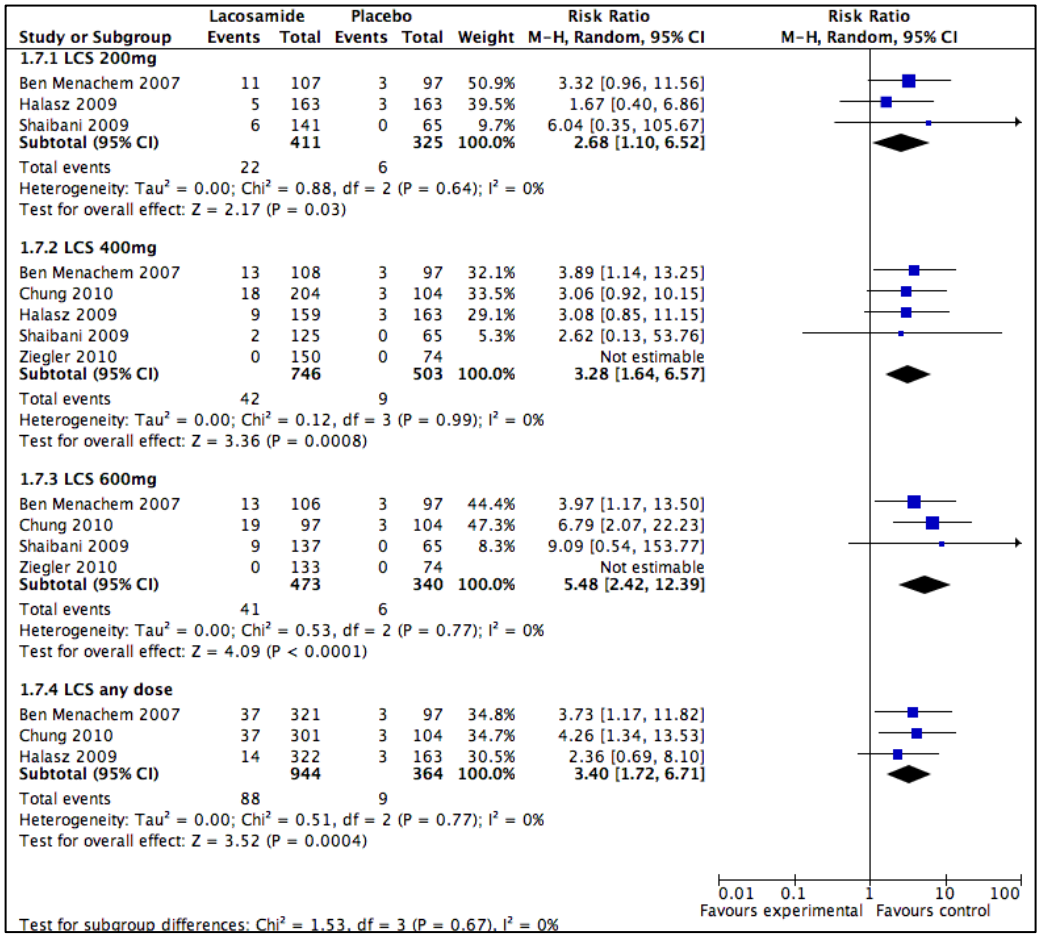

Figure 88 Proportion of patients with Vomiting across indications

For outcome vomiting, three epilepsy trials (Halasz 2009, Ben-Menachem 2007 and Chung 2010) and two neuropathy trials (Shaibani 2009 and Ziegler 2010) were included. Tau squared values were low for all subgroups and p-values for chi squared were not significant. Therefore, there is no significant heterogeneity for outcome vomiting.

Null hypothesis is true for this outcome.

8.8.12 Withdrawals due to Adverse Events: Meta-analysis using the Random effects model

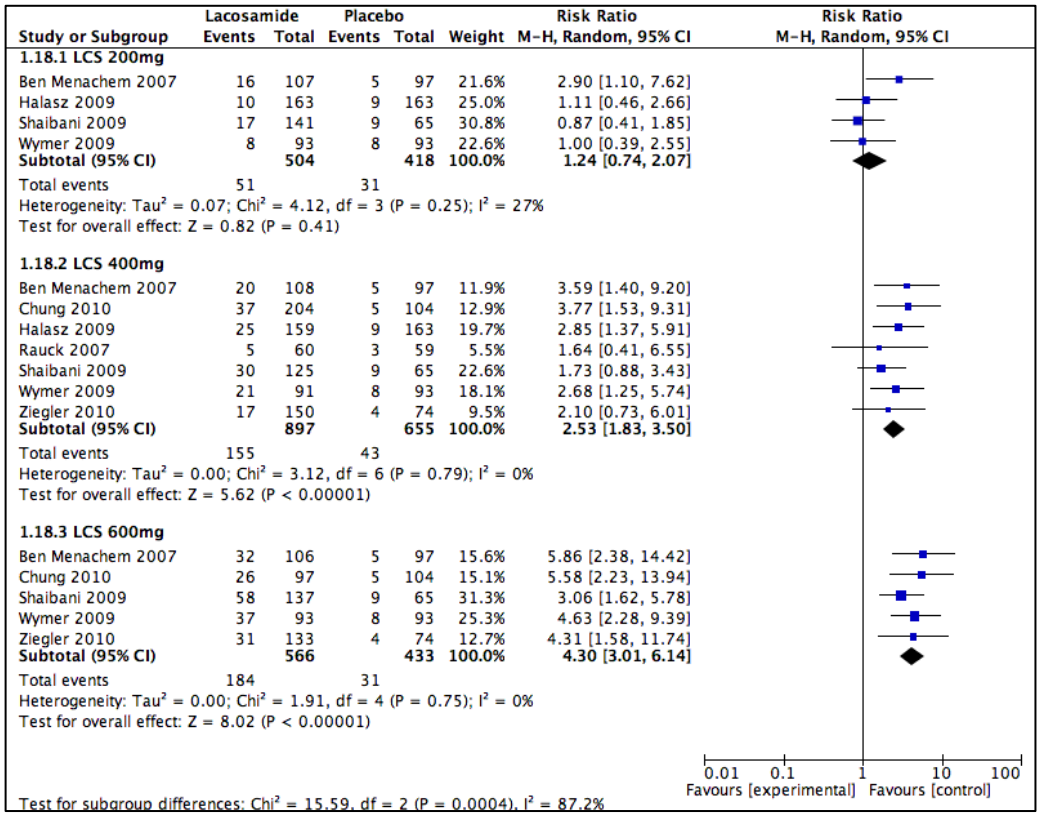

Figure 89 Proportion of patients withdrawing due to adverse events across indications

For tolerability outcome of withdrawals due to adverse events, three epilepsy trials (Halasz 2009, Ben-Menachem 2007 and Chung 2010) and four neuropathy trials (Rauck 2007, Shaibani 2009, Wymer 2009 and Ziegler 2010) were included.

Some heterogeneity was noted for the 200mg subgroups when we compared withdrawals due to harms. There were more withdrawals in Ben Menachem as compared to Halasz and the other two neuropathy trials (Shaibani 2009) (Wymer 2009). This could possibly be explained by random chance, as withdrawals were similar for the 400mg and 600mg subgroups.

Null hypothesis is true for this outcome.

8.9 Summary of Results

Comparisons with adverse event results from systemic reviews of lacosamide in epilepsy trials showed that fatigue was the only outcome that changed effect size to yield a significant result when neuropathy trials were combined was fatigue. For the 400mg dose of lacosamide, the summary measure was 2.0 (95% CI of 1.0 to 4.03) and this changed to 1.98 (95% CI of 1.11 to 3.52) when neuropathy trials were combined (figure 80). This is interesting as we used random effects models, had we used fixed effects model, then we would have expected the confidence intervals would have been narrower.

For outcome somnolence, there was no significant change in the overall summary measures. The effect sizes for somnolence in Shaibani (2009) ranged from 6.97 to 11.9 compared with 0.98 to 1.95 in the epilepsy trials; there was no overall change in the confidence intervals. A similar phenomenon occurred with outcome tremor where the effect sizes from the neuropathy trials were significantly greater but not enough to alter the overall result.

The following adverse events did not change substantially in effect size or confidence intervals: any adverse event; dizziness; headache: nasopharyngitis; nausea: vertigo and vision blurred.

A summary of the results is displayed in a table below (table 49 page 239). Only two outcomes were not possible to be summated, as the null hypothesis was not true. One can conclude that harms across indications for lacosamide can be utilised in meta-analyses across indications.

Outcome	Possible to combine effect sizes?
Any AE	Yes
Dizziness	Yes
Fatigue	Yes
Headache	Yes
Nasopharyngitis	**No**
Nausea	Yes
Somnolence	Yes
Tremor	**No**
Vertigo	Yes
Vision Blurred	Yes
Vomiting	Yes
Withdrawals	Yes

Table 49 Final summary of judgements for harms due to lacosamide

8.10 DISCUSSION

This chapter discussed adverse events across indications for lacosamide. Lacosamide is a novel antiepileptic drug that is used in neuropathy and epilepsy trials. Seven lacosamide trials were found with overall duration and design of trials to be similar. The only differences were attributable to clinical differences between patients. An important difference between the two groups of patients would be additional drugs taken by these patients in addition to the study drug. In the three epilepsy trials these may include other anticonvulsants. In the neuropathy trial patients, other anticonvulsants were barred from inclusion but antidepressants were allowed.

One would have expected that effect sizes would be dramatically different in all outcomes as there are significant clinical differences in trial populations. However, differences in effect sizes were seen in only two outcomes namely somnolence and fatigue. Patients recruited in neuropathy trials experienced more somnolence and fatigue compared to epilepsy patients. One can speculate these are due to clinical differences caused by an effect of add-on drugs used by patients. In epilepsy trials the add-on drugs were other AEDs and in the neuropathy trials patients were barred if they took anticonvulsants, but were allowed to take antidepressants. Therefore, one can envisage that neuropathy trials are essentially lacosamide monotherapy studies and a comparison of harms is made between the two. One would expect that harms would be

greater in the epilepsy trials, especially with regards to fatigue and somnolence but we find that the opposite is true. The reasons for this cannot be fully explained.

Fatigue and somnolence was greater in neuropathy trials compared to epilepsy trials and this may be reflective of clinical reasons- older age group and higher co-morbidities.

Only fatigue changed direction to reach statistical significance for the 400mg dose when data from neuropathy trials were summated.

Lacosamide patients in neuropathy trials were not allowed AEDs but were allowed to take antidepressants. Lacosamide patients in epilepsy trials are allowed to take other AEDs.

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Statistical tests of heterogeneity were used to compare if there was any in heterogeneity when trials were combined. It was demonstrated that the null hypothesis was true for all outcomes except nasopharyngitis and tremor. However, the null hypothesis was true for fatigue and somnolence largely because of wide confidence intervals. This is illustrative of the fact that statistical tests of heterogeneity like the chi-squared test have low power in detecting this. Therefore, one cannot completely rely on statistical tests of heterogeneity and other tests like the I-squared statistics and simply an observation of the effect sizes could be utilised in making judgements. Further tests, which can be used to explore heterogeneity, include meta-regression. However, this was not done in this chapter but will be explored in the next chapter.

8.11 Conclusions

- Harms across indications can be used for meta-analysis of lacosamide in systematic reviews and these can be meta-analysed by the usual method found in RevMan 5.0.
- Nineteen adverse events that were not reported in the epilepsy trials but were reported in the neuropathy trials. This clearly suggests that outcome reporting bias exists. This result is contrary to what was discussed in the previous chapter. These harms could have occurred in epilepsy patients too but were not reported in the unpublished epilepsy data. A recent study by Hodkinson et al compared the reporting of harms in journal publications and clinical study reports of orlistat (2014). The authors found that published journals report subset of harms and not the entirety of the data in clinical study reports (Hodkinson et al 2014 unpublished).
- The next question is if harms across indications can be used for the other antiepileptic drugs. This will be discussed in the next chapter.
- Only one harms outcome yielded a change in significance when harms from other indications were summated. This may be an important finding for may be due to chance.

Chapter 9

Harms across indications: Issues in Meta-analysis.

9.1 Introduction

From previous chapters, we learnt that adverse event data from lacosamide neuropathy trials could be used in systematic reviews for epilepsy. A number of differences were noted, some adverse events reported in neuropathy trials were not reported in epilepsy trials and vice versa. There were differences in the proportion of adverse events as well with some adverse events occurring more commonly in one trial than another. Despite some differences between trials, one can conclude that overall there was no significant heterogeneity between neuropathy and epilepsy trials and using these additional trials may provide additional harms data for analysis. This therefore raises the question if harms data from other indications can be incorporated in meta-analysis.

This chapter formulates a hypothesis of how harms form other indications could be used and this is followed by the methodological problems encountered and the results.

Several AEDs have been used in other indications. Broadly speaking these conditions include headache disorders and neuropathies. Headache conditions can be primary headache disorders like migraine or SUNCT (short lasting unilateral neuralgic headache and conjunctiva tearing) and some secondary headache disorders. Neuropathies that use AEDs include mostly diabetic neuropathy; idiopathic neuropathy or hereditary neuropathy. Description of every individual condition is beyond the scope of this thesis.

9.2 Hypothesis

Harms outcomes from trials of other indications could be summated in a meta-analysis if no or little significant statistical heterogeneity or variance exists in the effect sizes of adverse events. The null hypothesis could be defined in two ways:

$$H_0 = Q_i \text{ is low with } p > 0.05$$

Where H_0 is the null hypothesis, Q_i is the variance between indications and p is the significance level.

Alternatively, the variance of the trials is not different between indications:

$H_0 = R^2$ is low.

A description of R^2 is provided in later sections.

9.3 Aims

1. To determine if harms data from epilepsy trials can be included in summated with harms data from either neuropathy or headache trials.
2. To explore statistical methods used for analysis of harms across indications.
3. To test the hypothesis using meta-analysis and meta-regression methods (Prove in the null hypothesis).
4. To provide recommendations for further work.

9.4 Methods

9.4.1 Inclusion of AEDs

To analyse harms in other indications, trials in at least one non-epilepsy indications and one-epilepsy indications were used. This is because to summate the indications one would need at least one of each indication.

A list of AEDs that could be included is shown below. All of the AEDs with the exception of carisbamate are currently used in clinical practice. Some of the AEDs shown here may have had trials in other indications but are not in current clinical use for example topiramate is used in headache disorders, but is not used in neuropathic pain. Trials were selected regardless of whether they were in clinical use as any information on harms may be important.

	Headache Disorders	Neuropathic disorders
Lacosamide		✔
Topiramate	✔	✔
Lamotrigine	✔	✔
Gabapentin	✔	✔
Pregabalin		✔
Oxcarbazepine	✔	✔
Carisbamate	✔	
Valproate	✔	✔

Table 50 AEDs for inclusion

9.4.2 Clinical trials: Inclusion and Exclusion criteria

Trials conducted in adults or mixed age populations were used. Included trials would have to be placebo controlled as the comparator group. Trials published till 2011 were used, trials recruiting children were excluded as harms outcomes are reported poorly in these studies (Shukralla et al 2011). Trials excluded were those where the outcome was a neuropsychological outcome measure as these were secondary reports of other trials. Also excluded were observational studies as studies needed to have a placebo group.

9.4.3 Selection and searches of clinical trials

Search terms were: “epilepsy”, “headache” and “neuropathy” to search for trials across indications. Additional words used were “migraine” and “diabetic neuropathy”. Any trial that was not found via Medline was obtained from the Cochrane Register of Clinical Trials and the British Library. Given the large number of trials to be searched, inter-rater agreement statistical tests of selection of clinical trials were not carried out. No attempt was made to collect unpublished data as the anticipated number of trials was expected to be large, making it impossible to contact all relevant study sponsors. Selected studies were catalogued and data extracted from them.

9.4.4 Data extraction.

Only harms data and withdrawal data were collected, efficacy outcomes were not used as efficacy in not the focus of this thesis. Tolerability outcome such as withdrawal data was collected too.

Data extracted from trials included harms data and details of the clinical trial that was relevant to the research question. Details of trial, authors and dates of publication were collected. Harms data collected included proportion of patients with specific adverse events and proportion of patients that withdrew due to adverse events. Some trials would report the total number of patients that report any adverse events and this was extracted also.

This was an observational study of harms and therefore selection of trials, extraction of data and analysis was not blinded and was not subject to random allocation.

9.4.5 Outcomes measures

When choosing which adverse events to compare across trials, problems were encountered with nomenclature. Terms of harms may vary between studies. Trials may use different terminology to mean a specific harms outcome. An example of this is the outcome fatigue. Some trials report this as fatigue whereas others use the term asthenia. These two outcomes in theory could be considered synonymous. However, asthenia is also synonymous with weakness. There is no consensus if these outcomes can be summated into a single outcome called fatigue. To combine synonymous outcomes together would seem reasonable but this was not done, as there are no rules in deciding which outcomes are synonymous.

Thirty possible adverse events could be analysed however this would be an exhaustive task. Therefore, common harms were chosen and decided in a short list of harms shown below.

1. Dizziness
2. Ataxia
3. Headache
4. Fatigue
5. Nausea
6. Somnolence

Other harms outcomes were used included:

- Any adverse events (if outcome reported)
- Proportion of patients who withdraw due to adverse events (if outcome reported)

9.4.6 Outline of analysis

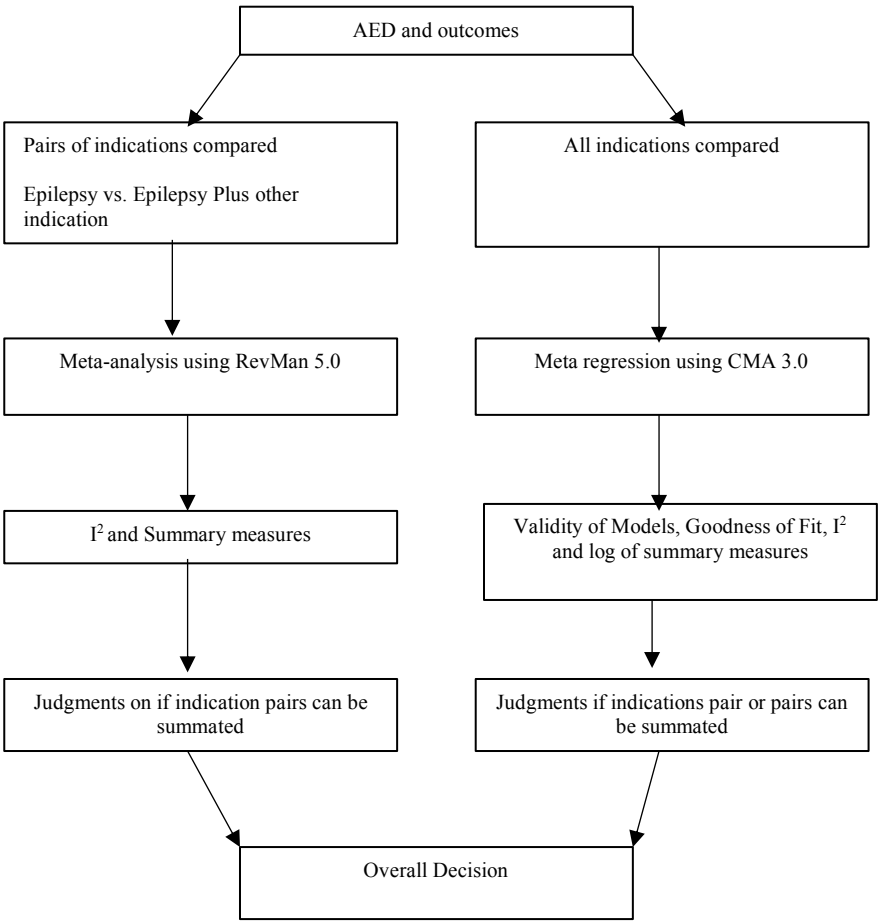


Figure 90 Outline if analysis methods used in exploring heterogeneity

To test the hypothesis, RevMan 5.0 and Comprehensive Meta-Analysis Version 3.0 (CMA 3.0) versions of software were used. RevMan was used to explore heterogeneity and CMA was used to explore heterogeneity further. Both methods were used to make a decision. An outline to the process is shown in the figure above. Details of meta-analysis and meta-regression have been discussed in earlier chapters.

Meta-analysis as a traditional method to explore heterogeneity lacks power and meta-regression is a useful way to explore any additional heterogeneity.

To test the hypothesis, comparisons between summary measures of epilepsy trials and measures from combined indication trials. Differences in effect sizes though visual inspection were commented upon and if there were any difference between them. A Student's t-test would not be sensitive to detect small differences when comparing differences in effect sizes. To compare any differences in heterogeneity, $I^{2,}$, Q statistics and Tau squared statistics to measure variance were used.

Summary effect measures and heterogeneity data for harms were generated using RevMan Version 5.0. The results and calculations are presented in a way where by summary measures of trials in epilepsy are displayed alongside summary measures with trials from two indications. Any differences were commented upon and if there existed any changes in I^2 scores. If there was a decrease in heterogeneity this suggests that any clinical differences between indications are mild and do not affect the summary measures. If there is no change in heterogeneity then there may be a good argument in combining summary measures and if there was an increase in heterogeneity then clinical differences exist to the extent that harms outcomes could not be combined.

9.4.7 Analyses using statistical tests of heterogeneity (RevMan 5.0)

Using RevMan 5.0 calculations of the relative risks of an adverse event compared to placebo were made. Wherever possible, these were sub-grouped by dose. If dose data was not available, any dose as the sub-group was used.

AEDs that were sub-grouped by dose were: pregabalin, topiramate and carisbamate. The other AEDs could not be sub-grouped by dose as these may have been non-overlapping (gabapentin) or reporting of trials was poor and did not have this data available for a significant number of studies.

Our aims are not to sub-total relative risks into summary measures, but to describe any heterogeneity and any variance in the effect sizes. We compared effect sizes when epilepsy trials were used for each dose and then compared the effect sizes when the trials from other indications are summated with those of epilepsy.

As discussed in chapter five, in-between study variance is given by the Tau statistic. This in-between study variance can be calculated in RevMan 5.0 and displayed as the Tau squared statistic (τ^2). Tau squared statistic is an indicator of the dispersion of the individual study effect size around the summary measure. If the precisions of the summary measures are wide and if the individual effect sizes are significantly varied, then this will not be reflected as a high tau squared value. Tau squared values can range from zero to 1.0.

Another way of describing the variance between the summary measures is the chi-squared statistic ($\chi 2$). If the chi squared value and the degrees of freedom are similar then the null hypothesis can be accepted as true This is interpreted by looking at he p-value and if p is > 0.10 then there is no variance in the summary measures.

As mentioned in chapter five, heterogeneity can be assessed by calculating $I^{2,}$ this is a measure of how much of the variance is real and how much of the variance is random error. Interpretation of finding was based on making qualitative judgments for each individual AED subgroup. If the values of tau or chi indicated no significant in-between study variance then this could indicate that trials across indications could be used with epilepsy trials. However, the only caveat to this is if the effect sizes differed in magnitude by a significant amount, this could indicate there may be some unexplained variance cause for this other than indication. We commented on effect sizes for harms in epilepsy trials and when epilepsy and other indications were combined.

The result of these was compared with the decisions from meta-regression and an overall decision was made.

9.4.8 Analyses using meta-regression (CMA version 3.0)

This complemented the earlier method. The aims of using meta-regression were to look for any other variance that could not be explained using RevMan.

Separate analyses for each AED and adverse events pair were carried out. Similar to RevMan, numbers of patients with adverse events in the active and control groups

were inputted to calculate an effect size. The software calculated the relative risks and the natural log of relative risks. The natural log of relative risk was used in the meta-regression analysis. The natural log of relative risks was the dependent variable and the indication was the independent variable. Other covariates that were inputted but were not analysed were dose and year of publication. The natural log of relative risk was a continuous variable and indication was a categorical variable. To carry out regression using categorical variables - indication was coded as dummy variables; 0 for epilepsy; 1 for neuropathy and 2 for headache.

A regression plot with a regression line was produced. Epilepsy was the reference group used in all analyses conducted. An example of the regression plot is shown in figure 91. From this figure, one can extract the test of the model Q with p values and the goodness of fit data.

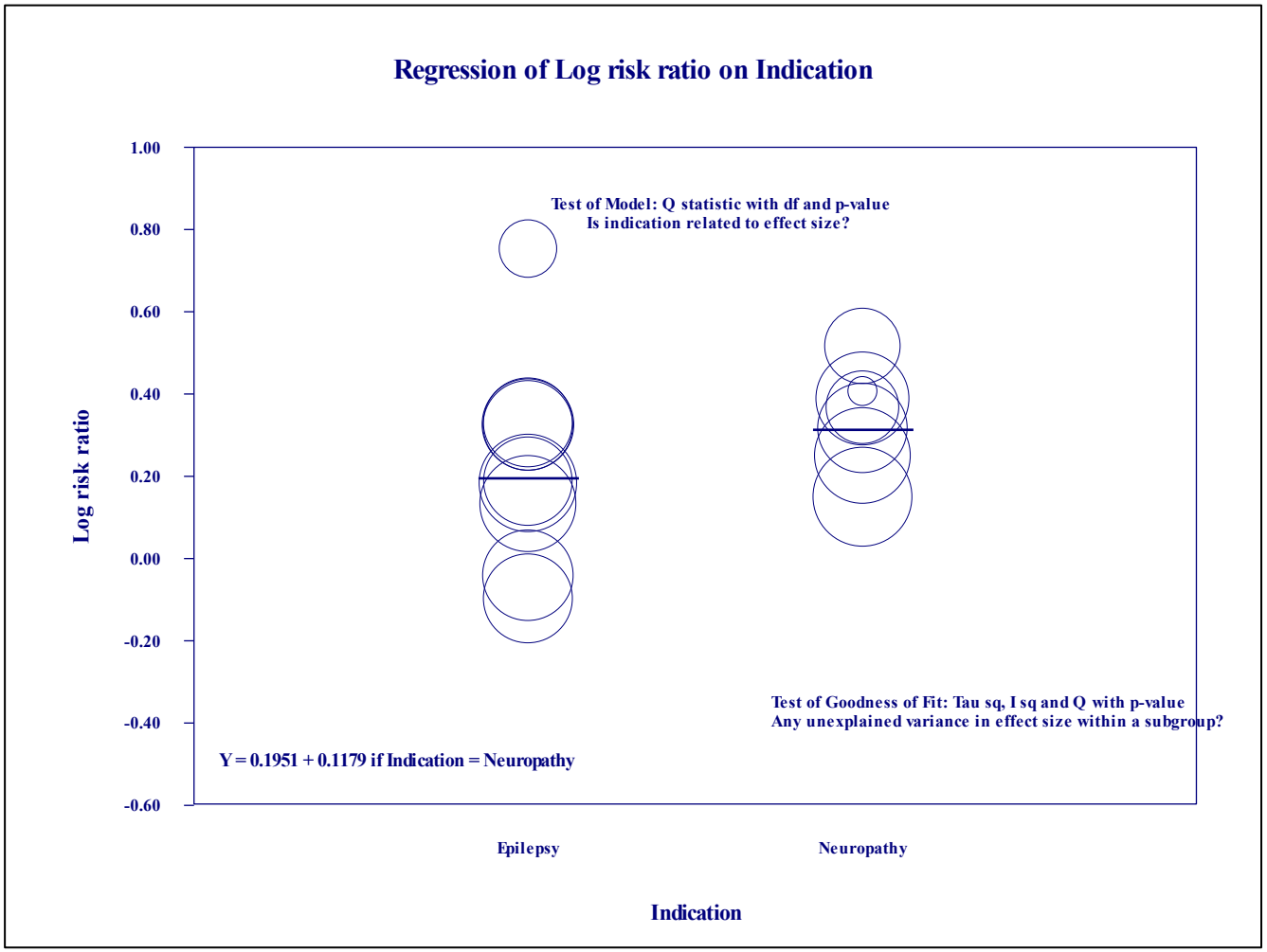


Figure 91 Example of Meta-regression scatter plot for categorical variables. Epilepsy is the reference variable and neuropathy is the test variable. The test of the Model is the Q statistic. Also illustrated are the goodness of fit & the regression equation

The output from the analysis would include the epilepsy and neuropathy studies plotted on the regression lines. The circles represent the studies in proportion to their weights. In the example above, there are two categorical covariates (epilepsy and neuropathy). The horizontal lines indicate the regression lines and they intercept with the corresponding value of the natural log of relative risk. The regression equation is shown in the bottom left side.

A Test of the Model was obtained. This is given by a Q statistic, the degrees of freedom and corresponding p-value. The degrees of freedom are the number of studies minus one. However, for this analysis there are two categorical variables (epilepsy and neuropathy) therefore the df is 1.0 and if all three indications were used the df is 2.0. If the p value is > 0.05 then the null hypothesis is true - that the variance of the effect sizes between the two indications is related to chance (hence trials across indications can be used). The test of the model tries to explain the variance between subgroups.

The Goodness of Fit is another analyses conducted. This is a test to determine if there is any unexplained variance within a subgroup and not between subgroups (within epilepsy or neuropathy). This could be interpreted as a measure of any unexplained variance that may still linger, for example like a dose interaction or any other factor. The outputs in a Goodness of Fit analyses are a Tau statistic, a Q statistic and its corresponding p value.

The output also includes an I^2 statistic, which gives a measure of the degree of variance that is explained and the degree of variance that is unexplained.

Also calculated was R^2. This is the proportion of the between studies variance (tau) explained by the model to the total variance of all the studies. R^2 can be defined as

$$R^2 = \frac{T^2_{Explained}}{T^2_{Total}}$$

Alternatively, R^2 can be defined as

$$R^2 = 1 - \frac{T^2_{Model}}{T^2_{Total}}$$

To test the hypothesis, the Q and p-values from the Test of the Model were used. The natural log of relative risks for each indication; the test of Goodness of Fit was only commented on when indicated. If the R^2 is a very low value this too can suggest that the null hypothesis is true.

9.4.9 How the results will be presented

Because many comparisons for each individual AED were carried out, for the interests of space, the raw data is included in appendix J on page 360.

Results from RevMan are presented first followed by the meta-regression results to arrive at the overall result.

9.4.9.1 Tests of heterogeneity

The RevMan analyses displays the AED, with the indication pairwise comparisons (either epilepsy with headache or epilepsy with neuropathy). Displayed here are the effect sizes (relative risks) as a pair for each outcome. The first number is the relative risk for epilepsy trials and the next is the relative risk when both indications are combined. A decision is made if relative risks are different or has changed significantly (either no change, increased or decreased). Next presented are changes in I^2 before and after indications are combined followed by a decision of any changes to the I^2 statistic has occurred. Next, we display the corresponding Tau squared, Chi squared statistics and p-values. Finally, presented are the corresponding tau squared, chi squared and corresponding p-values. A decision is then displayed on if the null hypothesis is accepted or rejected.

9.4.9.2 Meta-regression

Also presented are the results from meta-regression analyses. For each AED, presented are the natural log of the effect size (relative risk) for each indication followed by the

Q statistic of the model and the corresponding p-value of the model. Next presented are the Goodness of Fit data as a p-value, the I^2 squared of any unexplained variance and the R^2 ratio. This is followed by a judgement if the null hypothesis its true. Regression equations are not displayed, as these are only useful if we need to make predictions of effect size using covariates.

9.4.9.3 Overall decision matrix

Because two separate methods were used to either reject or accept the null hypothesis, one would need to summate the results to make a judgment of the overall result. This was displayed in a color-coded manner. The null hypothesis could both be accepted, rejected or, uncertain and colour coded accordingly.

9.5 Results

Analysis of harms across indications is a complex question that needed various methods to answer the hypothesis proposed. First, I will discuss the results of trial searches, then I will discuss the results of the analysis.

9.5.1 Searches for trials

Searches were carried out for seven placebo-controlled AED RCTs. We found one hundred and six trials in total. This included ninety-nine non-lacosamide trials and seven lacosamide studies. Included trials were placebo-controlled trials. Due to interests of time, we did not carry out any analysis of how data was extracted and there was no double blinding of data extraction process. A summary of the number of trials selected is shown in the table below and the details of these trials are shown in the appendix F on page 340.

AED	Epilepsy	Neuropathy	Headache	TOTAL
Carisbamate	2	0	1	3
Gabapentin	6	12	2	20
Lamotrigine	8	8	1	17
Pregabalin	5	15	0	20
Topiramate	11	2	7	20
Valproate	2	5	6	13
Oxcarbazepine	2	3	1	6
Lacosamide	3	4	0	7

Table 51 Number of epilepsy, neuropathy and headache trials included

9.5.2 Lacosamide

Seven trials of lacosamide were selected, three epilepsy trials and four neuropathy trials. Pairwise comparisons of relative risks using RevMan were made with epilepsy and neuropathy trials for 200mg, 400mg 600mg and any dose subgroups. For all harms outcomes in RevMan analyses the null hypothesis was found to be true, indicating there was no significant heterogeneity between effect sizes if neuropathy trials were combined.

However, meta-regression analyses were in agreement with the RevMan analyses except for outcome 'any adverse event' where the p-value of Q statistic was significant, indicating heterogeneity between the effect sizes of epilepsy and neuropathy.

Overall decision is shown below. The first column lists the harms outcomes, the next column displays the results from meta-analysis (MA) and the third column displays the results from meta-regression (MR).

It was deemed that the meta-regression analyses for 'any adverse event' accepted the null hypothesis but there was still some unexplained variance. Thus, this was coded uncertain. Overall the null is hypothesis is true for lacosamide and trials across indication can be meta-analysed.

Adverse Event	LCS MA	LCS MR	OVERALL
Any			
Ataxia			
Dizziness			
Fatigue			
Headache			
Nausea			
Somnolence			
Withdrawals			

LEGEND	LCS MA
Null is true	
Uncertian	
Null not true	

MA is meta-analysis and MR is meta-regression

Figure 92 Overall results of summating trials across indication for lacosamide

Table 52 Meta-analysis of epilepsy and neuropathy for lacosamide 200mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lacosamide (200mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.03- 1.00	No Δ	66%-39%	↓	0.00	0.19	2 & 3	Null hypothesis is true
		Dizziness	2.16 -2.03	No Δ	0% -0%	No Δ	0.00	0.84	2 & 4	Null hypothesis is true
		Ataxia	2.61-2.83	No Δ	48%-4%	↓	0.04	0.35	2 & 4	Null hypothesis is true
		Headache	1.37-1.14	No Δ	0%-0%	No Δ	0.00	0.72	2 & 4	Null hypothesis is true
		Fatigue	1.64-1.44	No Δ	0%-0%	No Δ	0.00	0.88	2 & 4	Null hypothesis is true
		Somnolence	1.21-1.81	No Δ	Na-30%	?	0.51	0.23	1 & 2	Null hypothesis is true
		Nausea	1.93-1.38	No Δ	22%-6%	↓	0.02	0.35	2 & 4	Null hypothesis is true
		Withdrawals	1.75-1.24	No Δ	52%-27%	↓	0.07	0.25	2 & 4	Null hypothesis is true

Table 53 Meta-analysis of epilepsy and neuropathy for lacosamide 400mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lacosamide (400mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.15-1.05	No Δ	NA-31%	?	0.00	0.22	1 & 5	Null hypothesis is true
		Dizziness	3.25- 2.22	No Δ	0%-0%	No Δ	0.00	0.98	3 & 7	Null hypothesis is true
		Ataxia	5.04-5.00	No Δ	0%-0%	No Δ	0.00	0.95	3 & 5	Null hypothesis is true
		Headache	1.47-1.20	No Δ	47%-22%	↓	0.06	0.22	3 & 7	Null hypothesis is true
		Fatigue	2.0-1.98	No Δ	0%-0%	No Δ	0.00	0.98	2 & 5	Null hypothesis is true
		Somnolence	1.70-1.71	No Δ	0%-0%	No Δ	0.00	0.48	2 & 4	Null hypothesis is true
		Nausea	2.43-1.83	No Δ	33%-17%	↓	0.06	0.30	3 & 7	Null hypothesis is true
		Withdrawals	3.29-2.53	No Δ	0%-0%	No Δ	0.00	0.79	3 & 7	Null hypothesis is true

Table 54 Meta-analysis of epilepsy and neuropathy for lacosamide 600mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lacosamide (600mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.32-1.16	No Δ	NA-59%	?	0.01	0.06	1 & 4	Null Hypothesis is true
		Dizziness	5.02-5.30	No Δ	0%-0%	No Δ	0.00	0.98	3 & 7	Null hypothesis is true
		Ataxia	6.74-7.55	No Δ	0%-0%	No Δ	0.00	0.94	2 & 4	Null hypothesis is true
		Headache	1.18-1.39	No Δ	0%-0%	No Δ	0.00	0.46	2 & 5	Null hypothesis is true
		Fatigue	3.84-2.97	No Δ	NA-0%	No Δ	0.00	0.57	1 & 3	Null hypothesis is true
		Somnolence	1.21-1.53	No Δ	0-39%	↑	0.29	0.19	1 & 3	Null hypothesis is true *
		Nausea	2.43-1.83	No Δ	33%-17%	↓	0.06	0.77	2 & 5	Null hypothesis is true
		Withdrawals	4.17-4.30	No Δ	0%-0%	No Δ	0.00	0.75	2 & 5	Null hypothesis is true

*Null is true but there may be an increase in statistical heterogeneity when trials across indications are combined.

Table 55 Meta-analysis of epilepsy and neuropathy for lacosamide any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lacosamide (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.2-1.19	No Δ	NA-0%	?	0.00	0.78	1 & 2	Null hypothesis is true
		Dizziness	3.67-3.35	No Δ	0%-13%	No Δ	0.02	0.33	3 & 4	Null hypothesis is true
		Ataxia	Outcome not reported							
		Headache	1.32-1.20	No Δ	0%-0%	No Δ	0.00	0.49	3 & 4	Null hypothesis is true
		Fatigue	Outcome not reported							
		Somnolence	1.14-1.37	No Δ	0%-0%	No Δ	0.00	0.87	2 & 3	Null hypothesis is true
		Nausea	2.36-2.12	No Δ	34%-5%	↓	0.01	0.37	2 & 4	Null hypothesis is true
		Withdrawals	Outcome not reported							

Table 56 Meta-regression lacosamide, all indications and outcomes

Outcome	Natural log of Relative Risk (ln RR)		Q statistic of Test of Model df = 1	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
Indication	Epilepsy	Neuropathy						
Any	0.19	0.07	4.16	0.04	0.1004	35%	0.41	Null hypothesis is true but there is still some unexplained variance.
Ataxia	1.30	1.25	0.5	0.65	0.4523	0%	0.00	Null hypothesis is true
Dizziness	1.26	1.14	0.3	0.58	0.414	3.4%	0.00	Null hypothesis is true
Fatigue	0.75	0.58	0.21	0.64	0.9380	0%	0.00	Null hypothesis is true
Headache	0.26	-0.02	2.09	0.15	0.7561	0%	0.00	Null hypothesis is true
Nausea	0.76	0.56	0.76	0.38	0.5589	0%	0.00	Null hypothesis is true
Somnolence	0.35	1.08	1.44	0.23	0.8018	0%	0.00	Null hypothesis is true
Withdrawals	1.18	0.89	0.95	0.33	0.03	47%	0.00	Null hypothesis is true

9.5.3 Pregabalin

Twenty trials of pregabalin were selected, five were epilepsy trials and fifteen were neuropathy trials. Pairwise comparisons of relative risks were made using RevMan with epilepsy and neuropathy trials. Dose groups used were 150mg, 300mg, 600mg and any dose subgroups when making comparisons.

Null hypothesis was not true for adverse event headache in the any dose subgroup. Indicating heterogeneity. Null hypothesis was true for outcome ataxia in the 150mg subgroup but there was a high Tau-squared statistic value, indicating heterogeneity.

Meta-regression analyses showed the null hypothesis was not true for headache and somnolence. Null hypothesis was true for any adverse event and dizziness but I^2 proportions showed unexplained variance. This is likely due to a dose interaction. Null hypothesis was true for outcomes fatigue, withdrawals due to AE, and ataxia.

Overall result is shown in the figure below. The null hypothesis was true for ataxia in the meta-regression but uncertain in the meta-analysis (for 150mg dose). For outcome dizziness and any adverse event the meta-regression showed unexplained variance. Null was not true for outcome headache indicating significant heterogeneity. Overall pregabalin cannot be used across indication as some common adverse events show significant heterogeneity whereas some do not.

Adverse Event	PGABA MA	PGABA MR	OVERALL
Any			
Ataxia			
Dizziness			
Fatigue			
Headache			
Nausea	no report	no report	no report
Somnolence			
Withdrawals			

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 93 Overall results for summating trials across indications for pregabalin

Table 57 Meta-analysis for epilepsy and neuropathy for pregabalin any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Pregabalin (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	3.52-3.01	No Δ	66%-44%	↓	0.00	0.22	2 & 7	Null hypothesis is true
		Dizziness	3.52-3.01	No Δ	0%-27%	No Δ	0.05	0.18	3 &1 3	Null hypothesis is true
		Ataxia	3.70-4.46	↑	0%-0%	No Δ	0.00	0.12	3 & 7	Null hypothesis is true
		Headache	0.62-0.87	No Δ	0%-56%	↑	0.13	0.005	4 & 14	Null hypothesis is not true
		Fatigue	1.82-1.47	No Δ	NE-0%	NE	0.00	0.55	1 & 5	Null hypothesis is true
		Somnolence	2.17-2.88	No Δ	0%-30%	No Δ	0.08	0.11	5 &19	Null hypothesis is true
		Nausea	Outcome not reported							
		Withdrawals	3.11-2.19	↓	0%-8%	No Δ	0.02	0.36	3 & 14	Null hypothesis is true

Table 58 Meta-analysis for epilepsy and neuropathy for pregabalin 150mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Pregabalin (150mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.07-1.09	No Δ	66%-44%	↓	0.01	0.17	2 & 3	Null hypothesis is true
		Dizziness	2.05-2,14	No Δ	0%-0%	No Δ	0.00	0.87	2 & 3	Null hypothesis is true
		Ataxia	1.70-2.64	↑	56%-52%	No Δ	0.98	0.12	2 & 3	Null hypothesis is true but there is heterogeneity
		Headache	0.54-0.69	No Δ	0%-0%	No Δ	0.00	0.60	2 & 5	Null hypothesis is true
		Fatigue	Outcome not reported							
		Somnolence	1.29-1.73	No Δ	0%-0%	No Δ	0.00	0.47	2 & 6	Null hypothesis is true
		Nausea	Outcome not reported							
		Withdrawals	0.78-1.29	No Δ	64%-0%	↓	0.04	0.32	2 & 6	Null hypothesis is true

Table 59 Meta-analysis for epilepsy and neuropathy for pregabalin 300mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Pregabalin (300mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.14-1.25	No Δ	NA-59%	↑	0.02	0.12	1 & 2	Null hypothesis is true
		Dizziness	3.46-3.75	No Δ	NA-0%	No Δ	0.00	0.98	1 & 7	Null hypothesis is true
		Ataxia	3.33-3.18	No Δ	NA -0%	No Δ	0.00	0.72	1 & 5	Null hypothesis is true
		Headache	0.43-0.65	No Δ	NA-0%	No Δ	0.00	0.91	1 & 5	Null hypothesis is true
		Fatigue	Outcome not reported							
		Somnolence	1.62-3.38	↑	NA-24%	No Δ	0.10	0.25	1 & 7	Null hypothesis is true
		Nausea	Outcome not reported							
		Withdrawals	2.89-2.37	No Δ	NA-24%	No Δ	0.04	0.32	1 & 7	Null hypothesis is true

Table 60 Meta-analysis for epilepsy and neuropathy for pregabalin 600mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Pregabalin (600mg)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.38- 1.43	No Δ	NA- 28%	↑	0.00	0.30	1 & 7	Null hypothesis is true
		Dizziness	4.52-4.48	No Δ	0%-2%	No Δ	0.00	0.45	4 & 11	Null hypothesis is true
		Ataxia	4.49-5.03	No Δ	0%-0%	No Δ	0.00	0.85	4 & 6	Null hypothesis is true
		Headache	0.78-0.87	No Δ	0%-0%	No Δ	0.00	0.51	3 & 9	Null hypothesis is true
		Fatigue	Outcome not reported							
		Somnolence	2.56-3.57	↑	0%-21%	No Δ	0.06	0.24	4 & 11	Null hypothesis is true
		Nausea	Outcome not reported							
		Withdrawals	3.74-2.72	↓	0%-6%	No Δ	0.01	0.39	4 & 11	Null hypothesis is true

Table 61 Meta-regression Pregabalin all indications all outcomes

Outcome	Natural log of Relative Risk (ln RR)		Q statistic of Test of Model df = 1	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
Indication	Epilepsy	Neuropathy						
Any	0.19	0.31	1.98	0.1598	< 0.001	64%	0.04	Null hypothesis is true but there is variance still unexplained
Ataxia	1.25	1.92	3.41	0.06	0.786	0%	0.0	Null hypothesis is true
Dizziness	1.14	1.24	0.33	0.566	0.036	32%	0.0	Null hypothesis is true but there is variance still unexplained
Fatigue	0.60	0.46	0.05	0.826	0.763	0%	0.0	Null hypothesis is true
Headache	-0.42	0.06	7.43	0.0064	0.3062	11%	0.80	Null hypothesis is not true
Somnolence	0.69	1.26	8.05	0.0045	0.0751	27%	0.42	Null hypothesis is not true
Withdrawals	1.03	0.76	2.15	0.1422	0.3194	9%	0.34	Null hypothesis is true

9.5.4 Gabapentin

Twenty trials for gabapentin were selected, six were epilepsy studies, twelve were neuropathy studies and two were headache studies. Only the any dose subgroup was used, as there were no overlapping doses across indications.

The null hypothesis was not true for 'any adverse event' and dizziness outcomes in the epilepsy and headache comparisons. The null hypothesis was not true for the 'any adverse event' and headache outcomes in the epilepsy and headache comparisons.

Meta-regression showed the null hypothesis to be true for all outcomes except any adverse event and somnolence.

For outcomes 'any adverse event' and somnolence, the null hypothesis was not true. For outcomes headache and dizziness, theses showed significant heterogeneity in the meta-analyses but when used in meta-regression, the models failed to detect any heterogeneity. This cannot be fully explained, as there is no dose interaction here. it is thought that meta-regression methods are superior and therefore heterogeneity can be explained away using this model. Therefore to conclude, trials across indications for gabapentin cannot be used in meta-analysis due to non-overlapping dose and possible heterogeneity.

Adverse Event	GABA MA	GABA MA	GABA MR	OVERALL
Any				
Ataxia				
Dizziness				
Fatigue	no report			
Headache	no report			
Nausea				
Somnolence				
Withdrawals				
	Epi + HA	Epi + Neuro		

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 94 Overall results for summating trials across indications gabapentin

Table 62 Meta-analysis for epilepsy and headache gabapentin any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Gabapentin (any dose)	Epilepsy vs. Epilepsy and Headache	Any AE	1.27-1.37	No Δ	0-54%	↑	0.05	0.009	5 & 7	Null hypothesis is not true
		Dizziness	2.42-2.62	No Δ	0%-0%	No Δ	0.16	0.03	6 & 8	Null hypothesis is not true
		Ataxia	2.01-2.07	No Δ	0-29%	No Δ	0.33	0.30	3 & 4	Null hypothesis is true
		Headache								
		Fatigue								
		Somnolence	2.28-2.29	No Δ	0%-0%	No Δ	0.00	0.83	6 & 8	Null hypothesis is true
		Nausea	0.89-1.12	No Δ	0-28%	No Δ	0.13	0.24	5 & 5	Null hypothesis is true
		Withdrawals	1.39-1.65	No Δ	22-0%	↓	0.00	0.60	3 & 5	Null hypothesis is true

Table 63 Meta-analysis for epilepsy and neuropathy gabapentin any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Gabapentin (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.27-1.30	No Δ	0%-51%	↑	0.05	0.02	5 & 12	Null hypothesis is not true
		Dizziness	2.42-2.88	No Δ	0%-0%	No Δ	0.04	0.51	5 & 12	Null hypothesis is true
		Ataxia	2.55-2.87	No Δ	51%-26%	↓	0.06	0.42	3 & 7	Null hypothesis is true
		Headache	0.73-1.12	No Δ	21%-43%	↑	0.42	0.08	5 & 9	Null hypothesis is not true
		Fatigue	1.64-1.62	No Δ	0%-29%	No Δ	0.14	0.19	4 & 9	Null hypothesis is true
		Somnolence	2.14-2.59	No Δ	0%-1%	No Δ	0.00	0.43	6 & 14	Null hypothesis is true
		Nausea	0.89-0.93	No Δ	0%-0%	No Δ	0.00	0.83	4 & 13	Null hypothesis is true
		Withdrawals	1.78-1.77	No Δ	17%-0%	↓	0.00	0.63	4 & 14	Null hypothesis is true

Table 64 Meta-regression for gabapentin

Outcome	Natural log of Relative Risk (ln RR)			Q statistic of Test of Model df = 2	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
	Epilepsy	Neuropathy	Headache						
Any	0.22	0.48	0.54		<0.01	0.4312	2%	0.98	Null hypothesis is not true
Ataxia	0.56	1.08	2.30	3.68	0.16	0.5009	0%	1.00	Null hypothesis is true
Dizziness	0.90	1.18	1.20	1.94	0.38	0.3285	10%	0.0	Null hypothesis is true
Fatigue	0.53	0.77	-0.03	2.36	0.31	0.5414	0%	0.0	Null hypothesis is true
Headache	0.00	-0.05	NA	0.04	0.84	0.4309	2%	0.0	Null hypothesis is true
Nausea	-0.07	0.25	1.39	4.20	0.13	0.9081	0%	0.0	Null hypothesis is true
Somnolence	0.71	1.26	1.18	8.23	0.02	0.0510	0%	1.0	Null hypothesis is not true
Withdrawals	0.77	1.26	0.63	3.11	0.21	0.5903	0%	0.0	Null hypothesis is true

9.5.5 Topiramate

Twenty trials of topiramate were selected, 11 were epilepsy trials, two were neuropathy trials and seven were headache trials. Only the 200mg and any dose were used as subgroups in meta-analysis for headache and epilepsy trials. For the headache and neuropathy trials, any dose was used.

Pairwise comparisons epilepsy and headache and epilepsy with neuropathy gave differing results. Adverse events were poorly reported in trials for headache and therefore a number of comparisons could not take place. For any adverse event, dizziness and withdrawals the null hypothesis was not true but this was true for somnolence and nausea. In neuropathy comparisons, we did not find any heterogeneity between indications. One cannot explain why there is unexplained variance between headache and epilepsy even when dose is taken into account.

Meta-regression analyses showed that overall the null hypothesis is true but there may be dose interaction between indications and this makes sense, as topiramate doses used in headache is lower than doses used for seizures.

Overall topiramate cannot be used across indications due to heterogeneity in effect sizes and a possible dose interaction.

Adverse Event	TOP MA	TOP MA	TOP MR	OVERALL
Any				
Ataxia	no Report	no Report	no Report	no Report
Dizziness				
Fatigue	no Report	no Report	no Report	no Report
Headache	no Report			
Nausea				
Somnolence				
Withdrawals				
	Epi +HA	Epi + Neuro		

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 95 Overall results for summating trials across indications topiramate

Table 65 Meta-analysis for epilepsy and headache for topiramate any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Topiramate (any dose)	Epilepsy vs. Epilepsy and Headache	Any AE	1.05-1.34	No Δ	0%-80%	↑	0.04	0.001	3 & 4	Null hypothesis is not true
		Dizziness	1.23-1.13	No Δ	41%-30%	No Δ	0.06	0.18	4 & 8	Null hypothesis is not true
		Ataxia	Outcomes not reported							
		Headache								
		Fatigue								
		Somnolence	1.73-1.76	No Δ	40% -18%	↓	0.04	0.27	7 & 11	Null hypothesis is true
		Nausea	2.18-1.60	↓	0%-0%	No Δ	0.00	0.62	2 & 8	Null hypothesis is true
		Withdrawals	2.03-2.07	No Δ	23%-24%	No Δ	0.11	0.19	10 & 16	Null hypothesis is true

Table 66 Meta-analysis for epilepsy and headache for topiramate 200mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Topiramte (200mg)	Epilepsy vs. Epilepsy and Headache	Any AE	0.57-1.71	↑	NA-90%	↑	1.9	0.002	1 & 2	Null hypothesis is not true
		Dizziness	Outcomes not reported							
		Ataxia								
		Headache								
		Fatigue								
		Somnolence	3.11-3.31	No Δ	NA-0%		0.00	0.84	1 & 2	Null hypothesis is true
		Nausea	Outcomes not reported							
		Withdrawals	1.75-2.55	↑	NA-90%	↑	1.14	<0.001	1 & 3	Null hypothesis is not true

Table 67 Meta-analysis for epilepsy and neuropathy for topiramate any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Topiramate (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.05-1.10	No Δ	0%-0%	No Δ	0.00	0.70	3 & 4	Null hypothesis is true
		Dizziness	1.35-1.31	No Δ	37%-17%	↓	0.03	0.29	7 & 9	Null hypothesis is true
		Ataxia					Outcome not reported			
		Headache	0.85-0.84	No Δ	46%-33%	No Δ	0.05	0.16	6 & 8	Null hypothesis is true
		Fatigue					Outcome not reported			
		Somnolence	1.73-1.76	No Δ	40% -18%	↓	0.00	0.44	7 & 11	Null hypothesis is true
		Nausea	2.18-1.84	No Δ	0%-0%	No Δ	0.00	0.94	2 & 3	Null hypothesis is true
		Withdrawals	1.96 -1.94	No Δ	3%-28%	No Δ	0.23	0.19	8 &10	Null hypothesis is true

Table 68 Meta-regression for topiramate

Outcome	Natural log of Relative Risk (ln RR)			Q statistic of Test of Model df = 2	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
	Epilepsy	Neuropathy	Headache						
Any	0.13	0.13	0.45	2.63	0.27	<0.01	78%	0.0	Null is true but unexplained varaince
Dizziness	0.27	0.33	-0.05	1.43	0.49	0.2707	15%	0.0	Null hypothesis is true
Headache	0.20	-0.26	NA	1.19 [df 1]	0.28	0.0386	45%	0.0	Null hypothesis is true
Nausea	0.78	0.54	0.47	0.18	0.91	0.7539	0%	0.0	Null hypothesis is true
Somnolence	0.78	1.07	0.48	1.17	0.56	0.0940	32%	0.0	Null hypothesis is true
Withdrawals	0.84	0.48	0.90	0.51	0.77	0.0003	55%	0.0	Null hypothesis is true but there is still some unexplained variability

9.5.6 Lamotrigine

Seventeen lamotrigine trials were selected, eight were epilepsy trials, eight were neuropathy trials and one was a headache trial. Pairwise comparisons were made with epilepsy and neuropathy; epilepsy and headache trials.

Comparing epilepsy and neuropathy trials for lamotrigine, the null hypothesis was not true for any adverse events and somnolence. Fatigue was not reported in these trials. Null hypothesis was true with regards to the other outcomes.

Comparing epilepsy and headache trials, the null hypothesis was not true for any adverse event. Ataxia, headache and fatigue were not reported in these trials. All other outcomes, the null hypothesis was true.

Meta-regression of harms outcomes across indications showed for any adverse event was true or all except for 'any adverse event'.

Overall harms across indications for lamotrigine is a viable option given there was no heterogeneity for all outcome except any adverse event.

Adverse Event	LTG MA (N)	LTG MA (H)	LTG MA	OVERALL
Any				
Ataxia		no report		
Dizziness				
Fatigue		no report		
Headache		no report		
Nausea				
Somnolence				
Withdrawals				
	Epi+ Nuero	Epi + HA		

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 96 Overall results for summating trials across indications lamotrigine

Table 69 Meta-analysis for epilepsy and neuropathy for lamotrigine any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lamotrigine (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE	1.33-1.29	No Δ	76%-60%	No Δ	0.03	0.01	4 & 9	Null hypothesis is not true
		Dizziness	2.5-2.17	No Δ	30%-33%	No Δ	0.12	0.15	8 & 11	Null hypothesis is true
		Ataxia	2.46-2.49	No Δ	47%-34%	No Δ	0.25	0.18	8 & 11	Null hypothesis is true
		Headache	1.22-1.18	No Δ	0%-0%	No Δ	0.00	0.89	8 & 11	Null hypothesis is true
		Fatigue	Outcome not reported							
		Somnolence	1.65-1.64	No Δ	23%-58%	↑	0.49	0.006	8 & 12	Null hypothesis is not true
		Nausea	1.86-1.67	No Δ	0%-0%	No Δ	0.00	0.87	6 & 10	Null hypothesis is true
		Withdrawals	4.11-2,18	↓	0%-8%	No Δ	0.05	0.37	6 & 14	Null hypothesis is true

Table 70 Meta-analysis for epilepsy and headache for lamotrigine any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Lamotrigine (any dose)	Epilepsy vs. Epilepsy and Headache	Any AE	1.34-1.38	No Δ	68%-64%	No Δ	0.04	0.04	4 & 5	Null hypothesis is not true
		Dizziness	2.34-2.28	No Δ	18%-7%	No Δ	0.07	0.25	7 & 8	Null hypothesis is true
		Ataxia	Outcome not reported							
		Headache								
		Fatigue								
		Somnolence	1.65-1.73	No Δ	23%-17%	No Δ	0.12	0.29	8 & 9	Null hypothesis is true
		Nausea	1.85-1.76	No Δ	0%-0%	No Δ	0.00	0.60	5 & 6	Null hypothesis is true
		Withdrawals	5.09-4.47	No Δ	0%-0%	No Δ	0.09	0.31	8 & 9	Null hypothesis is true

Table 71 Meta-regression for lamotrigine

Outcome	Natural log of Relative Risk (ln RR)			Q statistic of Test of Model df = 2	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
	Epilepsy	Neuropathy	Headache						
Any AE	0.41	0.13	-0.17	2.86	0.24	0.0093	63%	0.0	Null hypothesis is not true
Ataxia	1.12	1.25	NA	0.01	0.95	0.1438	40%	0.0	Null hypothesis is true
Dizziness	1.07	0.44	NA	1.60	0.45	0.1844	27%	0.0	Null hypothesis is true
Headache	0.25	-0.04	NA	0.32	0.53	0.9047	0%	0.0	Null hypothesis is true
Nausea	0.56	0.24	2.04	1.70	0.43	0.8804	0%	0.0	Null hypothesis is true
Somnolence	0.52	0.40	1.69	0.59	0.74	0.1028	36%	0.13	Null hypothesis is true
Withdrawals	1.55	0.63	1.06	3.97	0.14	0.4522	0%	1.0	Null hypothesis is true

9.5.7 Oxcarbazepine

Six trials of oxcarbazepine were selected, two were epilepsy trials, three were neuropathy trials and one headache trial.

Pairwise comparisons using meta-analysis showed that null hypothesis was true for all outcomes except for any adverse events. Meta-regression showed that all outcomes except headache and any adverse events accepted the null hypothesis. Residual heterogeneity was present for withdrawals due to harms.

Overall harms across indications cannot be used as some outcomes were heterogeneous and others were not.

Adverse Event	OXY MA	OXY MA	OXY MR	OVERALL
Any	no report			
Ataxia	no report			
Dizziness				
Fatigue				
Headache		no report		
Nausea				
Somnolence				
Withdrawals				

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 97 Overall results for summating trials across indications oxcarbazepine

Table 72 Meta-analysis for epilepsy and neuropathy for oxcarbazepine any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Oxcarbazepine (any dose)	Epilepsy vs. Epilepsy and Neuropathy	Any AE			Outcome not reported					
		Dizziness	2.36-3.03	No Δ	8%-50%	↑	0.08	0.19	2 & 4	Null hypothesis is true
		Ataxia			Outcome not reported					
		Headache	1.13-1.46	No Δ	0-58%	↑	0.17	0.07	2 & 4	Null hypothesis is true
		Fatigue	2.14-2.21	No Δ	0%-0%	No Δ	0.00	0.62	2 & 3	Null hypothesis is true
		Somnolence	3.82-4.12	No Δ	49%-51%	No Δ	0.20	0.17	2 & 3	Null hypothesis is true
		Nausea	2.86-2.93	No Δ	0%-0%	No Δ	0.00	0.85	2 & 4	Null hypothesis is true
		Withdrawals	3.60-4.02	No Δ	28%-0%	↓	0.00	0.85	2 & 4	Null hypothesis is true

Table 73 Meta-analysis for epilepsy and headache for oxcarbazepine any dose

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Oxcarbazepine (any dose)	Epilepsy vs. Epilepsy and Headache	Any AE	1.20-2.43	↑	0%-96%	↑	0.20	0.001	2 & 3	Null hypothesis if not true
		Dizziness	2.36-2.41	No Δ	8%-0%	No Δ	0.02	0.62	2 & 3	Null hypothesis is true
		Ataxia	3.81-2.51	↓	NA -0%	No Δ	0.00	0.54	1 & 2	Null hypothesis is true
		Headache			Outcome not reported					
		Fatigue	2.14-2.32	No Δ	0%-0%	No Δ	0.00	0.50	2 & 3	Null hypothesis is true
		Somnolence	3.82-2.12	↓	49%-43%	No Δ	0.01	0.40	2 & 3	Null hypothesis is true
		Nausea	2.86-2.96	No Δ	0%-0%	No Δ	0.04	0.10	2 & 3	Null hypothesis is true
		Withdrawals	3.60-3.24	No Δ	28%-25%	No Δ	0.01	0.09	2 & 3	Null hypothesis is true

Table 74 Meta-regression for oxcarbazepine

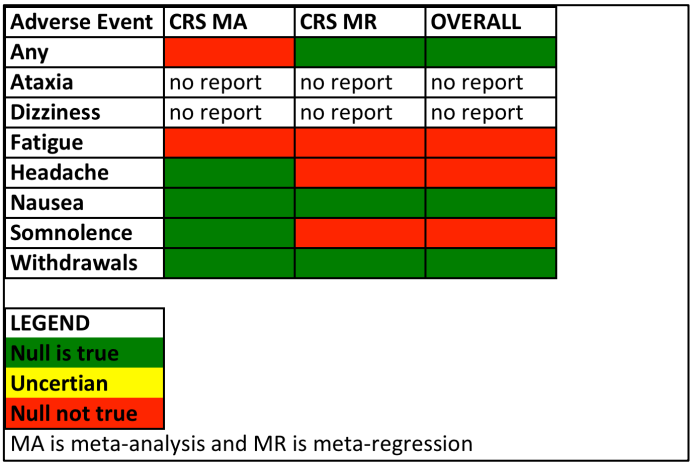
Outcome	Natural log of Relative Risk (ln RR)			Q statistic of Test of Model df = 2	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
	Epilepsy	Neuropathy	Headache						
Any AE	0.18	NA	2.60	30.5	<0.01	0.2370	28%	0.95	Null hypothesis is not true
Ataxia	1.44	NA	0.95	0.23	0.63	0.0720	57%	0.0	Null hypothesis is true
Dizziness	1.20	1.98	1.04	5.18	0.07	0.1960	28%	0.53	Null hypothesis is true
Fatigue	1.67	1.89	1.75	0.4	0.45	0.45	10%	0.0	Null hypothesis is true
Headache	0.18	0.73	NA	4.18 [df 1]	0.04	0.6129	0%	1.0	Null hypothesis is not true
Nausea	1.02	0.96	1.25	0.23	0.89	0.3373	12%	0.0	Null hypothesis is true
Somnolence	0.84	0.93	0.15	1.55	0.46	0.3098	15%	0.0	Null hypothesis is true
Withdrawals	1.63	1.51	0.74	0.62	0.74	<0.001	80	0.0	Null hypothesis is true but unexplained variability

9.5.8 Carisbamate

Three trials of carisbamate were selected. Two were epilepsy trials and one headache trial. Carisbamate was not awarded a licence in either indication due to a significant placebo treatment effect. Dose ranges of carisbamate include 100mg 200mg 300mg 400mg 500mg and 600mg tablets. However only the 100mg and 300mg doses were evaluable, as these were the two overlapping doses found in epilepsy and headache. Ataxia and dizziness were not reported in any of the trials.

The null hypothesis was not true for outcome 'any adverse event' for the 100mg dose using meta-analyses methods. The null hypothesis was not true for outcomes fatigue, headache and somnolence.

Overall harms across indications cannot be used for carisbamate.



Adverse Event	CRS MA	CRS MR	OVERALL
Any			
Ataxia	no report	no report	no report
Dizziness	no report	no report	no report
Fatigue			
Headache			
Nausea			
Somnolence			
Withdrawals			

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 98 Overall results for summating trials across indications carisbamate

Table 75 Meta-analysis for epilepsy and headache for carisbamate 100mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Carisbamate (100mg)	Epilepsy vs. Epilepsy and Headache	Any AE	1.19-0.97	No Δ	NA-0%	No Δ	0.00	0.66	1 & 2	Null Hypothesis is true
		Dizziness	Outcomes not reported							
		Ataxia								
		Headache	1.2-0.89	↓	NA-45%	↑	0.29	0.18	1 & 2	Null hypothesis is true
		Fatigue	2.08-1.97	No Δ	NA-0%	No Δ	0.00	0.94	1 & 2	Null hypothesis is not true
		Somnolence	1.79-1.38	No Δ	NA -6%	No Δ	0.02	0.30	1 & 2	Null hypothesis is true
		Nausea	1.04-1.08	No Δ	Na-0%	No Δ	0.00	0.93	1 & 2	Null hypothesis is true
		Withdrawals	0.58-0.85	No Δ	NA-0%	No Δ	0.00	0.37	1 & 2	Null hypothesis is true

Table 76 Meta-analysis for epilepsy and headache for carisbamate 300mg

Drug	Pair of indications	Outcome	Change in effect size before and after		Change in I^2 before and after		Tau^2	P-value of Chi^2	Number of trial pairs	Result
			Magnitude	Judgment	Magnitude	Judgment				
Carisbamate (300mg)	Epilepsy vs. Epilepsy and Headache	Any AE	2.60-1.56	↓	NA-82%	↑	0.43	0.02	1 & 2	Null hypothesis is not true
		Dizziness	Outcomes not reported							
		Ataxia								
		Headache	0.90-0.84	No Δ	NA-0%	No Δ	0.00	0.33	1 & 2	Null hypothesis is true
		Fatigue	4.63-3.19	↓	NA- 0%	No Δ	0.00	0.56	1 & 2	Null hypothesis is true
		Somnolence	1.91-1.42	No Δ	NA-18%	No Δ	0.08	0.27	1 & 2	Null hypothesis is true
		Nausea	1.87-1.34	No Δ	NA-22%	No Δ	0.08	0.26	1 & 2	Null hypothesis is true
		Withdrawals	0.69-0.79	No Δ	NA-0%	No Δ	0.00	0.71	1 & 2	Null hypothesis is true

Table 77 Meta-regression for carisbamate

Outcome	Natural log of Relative Risk (ln RR)		Q statistic of Test of Model df = 1	P value of Model	P value of Goodness of Fit	I^2 (Variance of data explained by model as being real)	R^2 Ratio of variance explained by model divided by total variance	Result
Indication	Epilepsy	Headache						
Any	-0.0165	0.0361	0.86	0.3610	0.9806	0%	0.00	Null hypothesis is true
Fatigue	0.33	1.14	5.65	0.0203	0.4101	3%	0.95	Null hypothesis is not true
Headache	0.17	-0.97	7.73	0.0055	0.3613	9%	0.9	Null hypothesis is not true
Nausea	0.20	0.14	0.04	0.8468	0.5172	0%	0.0	Null hypothesis is true
Somnolence	0.81	-0.42	8.83	0.0030	0.9594	0%	0.0	Null hypothesis is not true
Withdrawals	0.11	0.01	0.09	0.7661	0.2874	17%	0.0	Null hypothesis is true

9.5.9 Valproate

Harms outcomes in valproate trials were poorly reported. None of the outcomes were heterogeneous but one cannot make any judgments due to the paucity of data.

Adverse Event	VPA MA	VPA MA	VPA MR	Overall
Nausea				
Somnolence				
Withdrawals				

LEGEND
Null is true
Uncertian
Null not true

MA is meta-analysis and MR is meta-regression

Figure 99 Overall results for summating trials across indication for valproate

9.6 DISCUSSION

This chapter discussed the use of meta-regression as an additional method of exploring heterogeneity. Comprehensive meta-analysis version 3.0 is a novel method whereby two or more categorical covariates can be meta-analysed. Two distinct methods were used to investigate heterogeneity. The first method utilised Higgins's I^2 statistics and other tests of heterogeneity. In this method, comparative changes to heterogeneity before and after indications were combined and the results commented upon. This was a pragmatic method and judgments were made if harms across indications could be meta-analysed. For the second method, meta-regression was used to further explore heterogeneity. Both methods yielded similar results. We found that for some antiepileptic drugs, there was satisfactory agreement between meta-analysis and meta-regression methods. This was true for lacosamide, lamotrigine, oxcarbazepine, topiramate and gabapentin. Valproate was not evaluable due to poor outcome reporting. There were merits to the meta-regression method over meta-analysis method. The former method allows all three indications to be analysed and if dose was an interaction then this is evident in the results. A dose interaction would arguably imply that harms across indications cannot be used.

The study by Majorowski et al showed that the greatest incidence of harms occurs during the titration phase of a trial (2006). This is an important finding as this implies that the duration of the trial may not be as significant as previously thought.

Lacosamide and lamotrigine were the two AEDs whose harms data could be used across indications. The methods employed in this chapter have not been used before to compare harms across indications. The work presented here was purely and exploratory to answer the hypothesis if harms can be used across indications. One can now surmise that the null hypothesis is true for lacosamide and lamotrigine only.

The results also showed that for AEDs like pregabalin and gabapentin there existed a significant dose interaction which explains a lot of the heterogeneity Also for these two AEDs the dose used in neuropathy may be very different to those used in epilepsy in routine clinical practice.

Therefore we conclude that lacosamide might represent a special case and possibly we can surmise the same for lamotrigine.

Further meta-analysis could be done for lamotrigine to explore rare side effects like rash using data form trials across indications.

Other significant source of heterogeneity is due to differences in data collection between studies. The frequency of follow up in trials may be very different in epilepsy trials as compared to say neuropathy trials. Also, trial protocol in an epilepsy trial would be very different from a neuropathy trial. This study shows that despite this some harms outcomes can still be summated.

It would be reasonable to suggest that a significant limitation of this study is that the duration of follow-up was not controlled for when summating trials. An epilepsy trial may not have the same follow-up as a headache trial and not all headache and epilepsy trial would be of the same duration. Nevertheless, we would hope that the finding of Majorowski et al would apply here in that the duration of the trial has no significant impact on the proportion of harms detected in RCTs (2005).

It was noted that several studies of AEDs for headache conditions did not report headache as an adverse event. Headache was reported as a common adverse event in many trials of epilepsy and neuropathy. When reviewing topiramate studies in neuropathy and epilepsy we see that the relative risk for headache is less than one. Indicating that compared to placebo, topiramate also has an analgesic effect.

It is possible that future antiepileptic drugs manufactured by drug sponsors would not vary significantly in doses. Additional AEDs may be needed to determine if the results can be replicated. Any further work would require collaboration with a statistician.

9.7 Conclusion

- Meta-analysis of harms from other indications is an important issue that needs further evaluation.
- Due to commercial interests in a given AED, additional trials during the lifetime of an AED's licence may not be forthcoming. Therefore, trials from other indications may fulfil this need as far as harms outcomes are concerned.
- The methodologies demonstrated here could be used to make decisions if significant heterogeneity exists and if this is not the case then harms outcome can be used to make a more precise estimate. As demonstrated in chapter nine, that for outcome fatigue a more precise estimate was obtained.
- Other potential sources of harms data could include trials of AEDs where the formulation of an AED is compared to placebo or pseudo placebo.

Chapter 10

Conclusion and further work

10.1 Adverse events of antiepileptic drugs

Epilepsy is a chronic condition that is commonly treated with antiepileptic drugs. There are currently several antiepileptic drugs available and this number is expected to grow. Clinicians therefore need to choose which antiepileptic drugs are best for their patients. This is usually reached by consultation with the patient and based on clinical need. The General Medical Council requires doctors to give a balanced discussion of harms. They state that serious risk of treatments be discussed even though the perceived risk is small (Consent & Guidance 2015). In order to have an informed discussion, a clinician must be able to correctly quantify the risk of treatment. Data pertaining to harm can be obtained from many sources of evidence like RCTs and observational studies.

Harms of antiepileptic drugs are common and they have a considerable impact on the lives of patients with epilepsy. Epilepsy is a chronic condition and the benefits of these drugs have to be balanced against potential risks. Information on the risks of treatment is varied making it difficult for clinicians to search for this type of data. Current sources of data pertaining to risks are usually obtained from randomised controlled trials and observational studies.

Randomised controlled trials are good sources of evidence for transient dose-related adverse events. Observational studies are better at longer-term adverse events. However, results from observational studies can be biased and effect sizes can be over inflated whereas randomised trials may provide less biased estimates. Systematic reviews can provide an additional source of harms data when harms outcome from several trials is meta-analysed to provide a more precise estimate.

Most harms are type A reactions and therefore occur during the titration period (Majkowski et la 2005). This does not automatically mean that observational studies have less a role in harms as one would need to consider the harms occur throughout the trial period with an understanding that most of these occur at the begins of drug

A number of significant barriers currently exist which can impede the reporting of harms in randomised controlled trials. Some of these are related to how trials are

conducted and some of the reasons are due to reporting practices of medical journals. Trial related factors include, inadequate methods of collecting harms data, lack of a validated tool like the AEP. Coding practices of harms reported in trials may vary, our analyses showed that the older clinical trial reported dictionaries but these were not reported in the more recent trials. I cannot explain why this is so but using lacosamide as an example, we see that some outcomes like 'ataxia' was reported in one epilepsy trial but two other epilepsy trials reported this as 'coordination abnormal'. Coding of harms of AEDs is heterogeneous. In a recent study, Perucca et al performed correlations between harms reported using the AEP (adverse event profile) and QOLIE-89 (Quality of life in epilepsy 89) (Perucca et al 2009). Five distinct classes of AE emerged from correlations and this has implications into how harms could be classified and clumped into novel categories thereby we can have uniformity of harms across trials. And finally, harms are poorly reported in journal possibly this is related to journal space.

10.2 Reporting of harms of antiepileptic drugs

Harms reporting in randomised trials were deemed to be poor by several authors and this was confirmed in several therapeutic areas (Ioannidis 2004). Many of these studies used the CONSORT extension of harms as a benchmarking tool. Consistently we have that adverse event reporting in RCTs is poor in several therapeutic areas. Overall there has been no change in adverse event reporting since the publication of the CONSORT guidelines. Poor reporting of harms can be predicted based on the journal of publication and in the source of funding. Empirical evidence shows that the conclusions in randomised controlled trials are more positive toward experimental interventions if funded by for profit organisations (Als-Nielsen et al 2003). Therefore, the role of funding in how harms are reported in RCTs was explored.

In this thesis CONSORT guidelines were used as a tool to assess the reporting of harms in randomised controlled trials of antiepileptic drugs. This work has not previously been endeavoured in epilepsy. The findings presented in this thesis demonstrate the poor reporting of harms in RCTs and this is consistent with other studies (Hodkinson et al 2013). There has been no improvement in reporting of harms since the publication of the CONSORT guidelines. However certain aspects of adverse

event reporting in epilepsy trials were better compared to other therapeutic areas, for example the inclusion of a table for adverse events was far superior. The results showed a significant effect of funding in reporting of harms where this was better in commercially funded trials. Journals that endorse CONSORT and trials that are commercially funded may report harms better than other studies. Reporting of harms in trials in children is considerably poorer as compared to the reporting of harms of outcomes in adults is clearly an area of great concern.

To raise awareness of this issue, several posters and platform presentations were presented in national and international meetings. These are listed in the appendix K page 378.____.

10.3 Lacosamide systematic review

Chapter 8 describes a systematic review of lacosamide. This AED is a novel drug used in the treatment of partial epilepsy. This systematic review highlighted a treatment effect caused by placebo. The 200mg dose was not significant compared to placebo in the intention to treat analysis. A meta-analysis showed that the 200mg was marginally superior to placebo and this was statistically significant. This therefore has implications for clinical practice as the 200mg dose could be prescribed with fewer side effects.

This review was important for harms as more precise estimates for adverse events were obtained. Examples of harms estimates that are more precise were: coordination abnormal, relative risk of 6.12 (95% CI of 1.94 to 19.4); diplopia, relative risk of 5.24 (95% CI of 2.49 to 11.24) and fatigue, relative risk of 2.11 (95% CI of 1.12 to 3.97).

Summary measures for harms generated in this review showed a significantly larger effect size compared to the efficacy outcomes. This was an interesting observation and this could be related to a placebo drift effect. The work shown here led to further exploration of harms across indications.

10.4 Harms across indications- the lacosamide example

The inclusion of additional trials into a meta-analysis could potentially improve the estimation of the effect sizes. If the number of studies included in meta-analysis were increased, this could certainly be of a beneficial value. In this thesis lacosamide was used as an example for analysing harms. Currently there are three placebo-controlled trials of lacosamide as add-on therapy for patients with epilepsy. The likelihood of another placebo-controlled trial using lacosamide as add on therapy is remote as the drug sponsor holds a licence for the next four years and therefore the sponsor does not have an incentive for funding another RCT. However, if data from RCTs of another indication of lacosamide were found, the data from this could be used. I found four lacosamide trials in neuropathy.

When harms data from neuropathy trials were added to epilepsy studies, I found a more precise and significant estimate was found for outcome fatigue. Also, a number of harms outcomes were reported in neuropathy trials and not reported in epilepsy trials. I did not find any significant heterogeneity between the two indications.

10.5 Harms of antiepileptic drugs: other AEDs

Following the lacosamide example, I explored if harms across indications can be used in other AEDs. I selected a number of AEDs, which were used in headache and neuropathy indications. Here I used the traditional method of meta-analysis and statistical tests of heterogeneity I also used meta-regression to further explore heterogeneity and test my hypothesis that harms across indications can be used for analysing harms.

The results showed that two AEDs namely lamotrigine and lacosamide can be used across indications. The implication of this work is that harms data of newer AEDs from other indications are invaluable source of additional data. Drug sponsors would want to maximise their revenue for a given AED by carrying out trials in other indications, therefore these trials are valuable for harms data. Such data would be valuable in systematic reviews as they can be utilised either in meta-analyses or described narratively.

10.6 Recommendations

This thesis received the support of a grant from NIHR. One of the intended outputs was to improve the reporting of harms in systematic reviews and develop new tools for Cochrane reviews in relations to harms analysis. The following recommendations can be made:

- Reporting of harms in randomised controlled trials is poor. To improve this one needs to raise awareness of this issue. This work was well received in neurology meetings.
- Several publications have found similar results of inadequate reporting of harms in other therapeutic areas. CONSORT extensions for harms have been used extensively to highlight this point. Many journals endorse CONSORT but subspecialty journals are lagging behind in this regard. It is noted that
- The CONSORT guidelines therefore need to be further developed where they can:
    - Be incorporated into the peer review process. This may encourage academia to adhere to CONSORT when drafting the trial report stage and also implement it at the trial design stage. To encourage academia to adhere to CONSORT at the trial design stage and not just at the reporting stage. CONSORT guidelines could be modified and simplified into a quick guide for prospective authors on journal websites.
    - Simplification of harms guidelines into a workable checklist that not only serves as a benchmarking tool but as a tool used by authors at the writing stage of a given article
    - Elements from the CONSORT guidelines be included into a novel 'risk of poor harms reporting tool' in RevMan
- Currently all trials need to be registered in clinicaltrials.gov before they start recruiting patients. This is a new prerequisite by the FDA and EMA. This is a major step forward. Unfortunately, many published trials cannot be directly linked to trials published in the clincialtrials.gov website. This is attributable to

multiple web entries from different centres for the same study. Therefore, this has to be simplified.

- Poor reporting of harms is still prevalent in epilepsy trials therefore one must try to obtain unpublished data from the drug sponsors when conducting systematic reviews.
- If an AED is used in another indication, drug sponsors should be asked to make available unpublished data from these additional trials too. Attempts should be made to meta-analyse this data and if they show significant heterogeneity, then adverse events from these additional trials could be commented on by authors of systematic reviews. Such efforts may give clinicians a more balanced overview of harms.
- If harms issues of AEDs are reported in several trials including trials across indications, one may consider a separate systematic review in the Cochrane database with harms as the primary outcomes.
- Currently the Cochrane Group seeks to simplify their product by making the review process simpler. One would expect that harms might play a secondary role if this was to occur. One must therefore balance the needs for progress in light of external competition with the need to be explicit on harms reporting. Cochrane protocols and reviews need to be simplified and modified to include harms data.
- Innovative statistical methods should be developed where harms from across indications can be further analysed. Comprehensive Meta-Analysis version 3.0 allowed the use of multiple regression using more than one covariate. Similar statistical methods and tools need to be developed for novel harms outcomes.

10.7 Further work

A significant amount of raw data was collected from randomised controlled trials as raw data. A portion of the data was analysed in chapter 10. The remainder of this data was passed on to my colleague Sarah Donegan who refined the statistical methods.

This thesis focused on randomised controlled trials. However a recent Cochrane review evaluated non-randomised studies of antidepressants in epilepsy (Maguire et al

2014). Although the quality of evidence from these studies may not be robust but in certain therapeutic areas where evidence is lacking there may be a role of using this evidence. Therefore, new methodologies need to be explored in this area.

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Appendix A: List of trials used in analyses of harms reporting in randomised controlled trials of antiepileptic drugs.

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Appendix B: An explanation of Cohen's Kappa Statistic

Cohen's Kappa is a statistic used to assess the extent of reproducibility and reliability between rates of categorical variables. Where:

$$\kappa = \frac{A\ observed - A\ expected}{1 - A\ expected}$$

Equation 1 Kappa Statistic

To calculate the values of $A_{expected}$ and $A_{observed}$, we used Cross tab function of SPPS version 21. Alternatively this can be calculated using the punnet square and formulas below. The values a, b c, and d represent the number of items extracted by each reviewer/reader.

		Reviewer B		
		Yes	No	TOTAL
Reviewer A	Yes	a	b	a + b
	No	c	d	c + d
		a + c	b + d	

The observed probability of agreement is based on the number of yes and no outcomes that were agreed out of the total:

Total is a + b + c + d

$A_{observed} = (a + b)/ (a+b+c+d)$

The expected probability is calculated as below

The probability that reader one will say yes is

$P_{reader\ one\ yes} = (a + b)/ (a+b+c+d)$

The probability that reader two will say yes is

$P_{reader\ two\ yes} = (a + c)/ (a+b+c+d)$

Conversely the probability of reader saying no is

$P_{reader\ one\ no} = (c + d)/ (a+b+c+d)$, $P_{reader\ two\ no} = (b + d)/ (a+b+c+d)$

Therefore, the probability of both parties saying yes is the product of the two:

$P_{yes} = P_{reader\ one\ yes} \times P_{reader\ two\ yes}$

Likewise, the probability of both parties saying no is:

$P_{no} = P_{reader\ one\ no} \times P_{reader\ two\ no}$

Therefore the $A_{expected}$ is the sum of the two:

$A_{expected} = P_{yes} + P_{no}$

Finaly the values of $A_{expected}$ and $A_{observed}$ are known, hence kappa can be calculated.

Cohen's Kappa is a statistic used to assess the extent of reproducibility and reliability between rates of categorical variables. It is based on the observed readings by two different observers on two different occasions with the proportion of agreements that would be expected by chance. Cohen's kappa is denoted by the Greek letter κ

Where:

$$\kappa = \frac{A\ observed - A\ expected}{1 - A\ expected}$$

Equation 2 Kappa Statistic

If there is complete agreement then $A_{observed} = 1$ and $\kappa = 1$

If there is no more agreement than expected by chance then $\kappa = 0$

Kappa values greater than 0.75 is taken as good agreement. Those between 0.4 and 0.75 is fair to good agreement and less than 0.4 as moderate to poor agreement.

		Reviewer B		
		Yes	No	TOTAL
Reviewer A	Yes	a	b	a + b
	No	c	d	c + d
		a + c	b + d	

Appendix C: Other items of data collected for CONSORT data

1. Name of study
2. PubMed Reference number
3. Journal
4. Year of publication
5. Type of study: Efficacy, safety or both
6. Mono-therapy, add-on or polytherapy trial
7. Types of seizures
8. Inclusion and exclusion criteria
9. Drugs used and dosages
10. Number of intervention arms
11. Number of authors
12. Source of funding
13. Number of centres
14. Multi-centre or single study
15. Number of patients randomised
16. Blinding: single, double or open label
17. Dose reduction allowed
18. Duration of baseline phase, maintenance phase and withdrawal phase
19. Number of patients in the ITT population
20. Number of intervention arms
21. Inclusion and exclusion criteria
22. Blinding
23. Primary outcomes
24. Secondary outcomes
25. Details of harms outcomes
26. Number of patients with adverse events
27. Serious adverse events
28. Proportion of patients withdrawn due to adverse events
29. Methods of ascertainment of adverse events: dairy, clinical interview, phone call or mixture of methods
30. Details of dictionary used
31. Harms reported above a threshold; 5% 10% or >10%

32. Adverse event scales used
33. Total number of words used in report dedicated to harms and total number of words in article

Appendix D: Student t-test

A t-test examines two samples and compared their means. The t-test compares the differences of the means with the difference variance of the samples. The t-static is therefore a ratio of the difference in means and the standard error of the difference between the means. The t-test can only be used if the data is normally distributed. The t-statistic is denoted by:

$$t = \frac{mean\ of\ sample\ a - mean\ of\ sample\ b}{\sqrt{Variance\ of\ sample\ a\ +\ variance\ of\ sample\ b}}$$

Equation 3 T-test

There are two types of t-tests, which could be used, one for comparing two independent groups of variables or two dependent groups of variables.

A p value of <0.05 indicates that the null hypothesis is not true and any observed differences between groups is not due to chance. However, even if a p value is statistically significant, the difference in values needs to be large enough to be considered clinically significant.

Appendix E: Pearson's Correlation

The strength of the relationship between variables is given by the R statistic. The values of R can range from -1.00 to 1.00. A value of zero indicated no relationship at all, a value of 1.0 indicated a perfect positive correlation and a value of 1.0 indicates a perfect negative correlation. Any values that are not 1 or 0 can be interpreted by categorically as suggested by Cohen (Cohen 1960).

Size of r	Strength of correlation
r = 0.1 to 0.29 or r = -0.1 to -0.29	Small
r = 0.3 to 0.49 or r = -0.3 to -0.49	Medium
r = 0.5 to 1 or r = -0.5 to -1	Large

Appendix F: List of trials included in analysing harms across indications

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Appendix G: Search strategy for randomised controlled trials of antiepileptic drugs

Search strategy to search for randomised controlled trials of antiepileptic drugs in MEDLINE

1. randomised controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

11. exp Epilepsy/

12. Seizures/

13. (epilep$ or seizure$ or convuls$).tw.

14. 11 or 12 or 13

Appendix H: Search strategy used to search for lacosamide trials.

Search strategy to search MEDLINE (Ovid). Based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials published in Lefebvre 1994.

1. randomised controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

11. exp Epilepsy/

12. Seizures/

13. (epilep$ or seizure$ or convuls$).tw.

14. 11 or 12 or 13

15. lacosamide.tw.

16. erlosamide.tw.

17. 15 or 16

Appendix I: Performa for data collection for harms

Ref	Date	□ C □In C □ In C □Rd □ Relevant □Not relevant

Name of Study					
Journal			**□ RCT □ RV □ Other**		
Year of publication		**□ Retrospective**	**□ Prospective**		
Scope	**□ Efficacy □ Safety □ Other**	**Setting: □ Inpt □ Outpts □Other**			
Type of therapy	**□ Mono tx □ Polytherapy □ Add on □ Other**				
Multicentre or single centre & sponsorship	**□ Multi Centre □ Single centre □ Industry □ non Industry/NR □ Not Clear □ Not Stated**				
Describe the patient population	**□ First Seizure □ Newly diagnosed epilepsy □ Chronic epilepsy □ Epilepsy type not categorized □ Both Chronic and new dx □ Focal epilepsy □ Generalized Epilepsy □ Both F & G □ Specific Syndrome □ Status epilepticus □ Children □ Adults □ Children and Adults**				
No of patients randomized		**No of patients in the safety population**		**No of pts in the ITT population**	
No of patients in the inf ITT population		**No of patients in the PPR population**			
Number of authors	**Number of contributors**	**No of tx key Auth publi**			
Number of centres					
Inclusion criteria					
Exclusion criteria					

Blinding chose one or more
□ Double blinded □ Single Blinded □ Open label □ Placebo controlled NO DS Both open and double blinded phases A AFS Both open and single blinded
□ Parallel arm, No of arms _____ □ Cross over □ Other □ Head to Head

Drugs used	**Dosage**	**Drug used**	**Dosage**

Dosing Policy **□ Fixed** **□ Clinical Practice** **□ Other**	**Drug selection** **□ Fixed** **□ Random** **□ Clinical practice** **□ Not stated**	**Evaluation period duration dit by?** NO DS Fixed NO DS Until pt exits NO DS Until last pt randomized NO DS Clinical practice □ Not stated	**Any dose reduction allowed?** **NO DS Y NO DS N**
Duration of study (time line for PP)		**Year of study commencement**	
Titration methods			

Duration of baseline Period		**Duration of extension phase**
Duration of titration period		
Duration of evaluation period	NO DS specific time NO DS as per Evaluation period A AFS specific time and or as per EP	**Duration of withdrawal phase**

Primary outcome measures	□ Seizure remission/control □ Treatment failure/retention □ Adverse effect □ Other	**Units**
2◦ outcome measures		**Units**

Other end points

A AFS Safety end points_____

A AFS Pharmacokinetic end points_____

A AFS _____

A AFS _____

A AFS _____

ADVERSE EVENTS
Excluding SAE (go to page)

Drug name and dose	N =

Name of event or SE	No of events	No of pts	Duration in days	%	Outcome	

Serious AE

Event descriptions

Number of events **Number of patients**

Outcome **□ Resolved** **□ Death** **□ Major morbidity squeal** **□ Minor sequel**

Event descriptions

Number of events **Number of patients**

Outcome **□ Resolved** **□ Death** **□ Major morbidity squeal** **□ Minor sequel**

Event descriptions

Number of events **Number of patients**

Outcome **□ Resolved** **□ Death** **□ Major morbidity squeal** **□ Minor sequel**

Method of ascertainment of Adverse events

□ Pt diary only

□ Clinical interview only

□Diary and interview **Diary and Phone**

□ Phone call only

□ Phone call and interview

□ Other
□ Not Stated

Physical exam?
□ Y
□ N

Comments made on the quality of reporting of AE
□ Y **□ N**

AE tabulation

□ WHOART
□ COSART
□ Other
□ Not stated

Timing of AE/SAE

□Screening phase **□ Phase or timing not mentioned**

□Baseline phase

□Titration phase

□Double blind randomization phase/ open label phase

□Withdrawal phase

□Cross over to new drug phase

□Phase not mentioned but stated in weeks/months give details

Did they use an adverse event scale and what was it?	**Systematic method on collection of AE**
Scale used? □ Y □ N **□ Likert** **□ Mild/Mod/Severe** **□ Other** **□ LEAP**	**□ Yes □ No □ Not Stated** **Systematic method on what is reported** **□ Yes □ No □ Not Stated**

Trestment of AE/SAE	**□ Trial drug withdrawn** **□ Pt withdrawn** **□ New Tx added** **□ trial drug dose changed** **□ patient crossed over to another arm** **□ Other** **□ Not Stated**
Were patients with AE included in ITT analysis?	□ Yes □ No

Presentation of AE results

Number of patients dropped out due to AE:
Arm 1 2 3
Were these followed up?
□Y □ N
Included in final analysis?
□ Y □ N

What denominator was used to calculate the percentage of pts having AE?

Drop outs or AE events shown in a randomization chart? □ Y □ N
Demographics chart? □ Y □ N
AE table? □ Y □ N
No of AE Events? □ Y □ N
No of Subjects having AE? □ Y □ N
Percentage of patients having AE? □ Y □ N

AE tabulated as:
□ Systems approach □ Symptom specific approach □ Other approach

List all the AE outcomes shown in paper	

Total Number of words in article

Total Number of words attributed to adverse events

Percentage

Brief results of Overall Study	**Did AE affect the results and recommendations**	
Limitation of study		

Other data collected in second Epi info file that is directly added to the computer without paper work

1. **Number of Add on drugs if relevant**
2. **AE reported by** >5% >10% or not stated
3. **Names of all add-on drugs used**
4. **Number of discrete AE reported**
5. **AE in abstract**-Y? N?

6. **Number of tables attributed to AE**
7. **Number of Serious adverse events (SAE) reported**
8. **Name of individual SAE**
9. **Number of patients with each SAE**
10. **SAE related to trial drug**- Yes? No? Yes some not all? Not Stated?
11. **Causality-** All AE reported? Only treatment emergent? Not stated?
12. **SAE**- Discussed separately? Not discussed separately?
13. **AE frequency compared to placebo**- Yes? No?
14. **Comments made on AE relationship with dose**-Yes? No?
15. **Statistics used to discuss AE-** Descriptive? Inferential? Both? Neither?
16. **Did adverse events change trial protocol**- Yes? No?
17. **AE discussed in discussion**- Yes with clinical and dose guidelines given? Yes, with clinical implications only? Yes, with dose implications only? AE not discussed at all?
18. **Trial identification code in Medline**
19. **Was AE the primary outcome?** Yes/No it was secondary outcome/ AE not outcome at all/ not stated
20. **Total number of adverse events recorded including placebo**
21. **Total number of patients reporting AE including placebo**
22. **Most common AE in trial drug 1** (name of event)
23. **Max percentage of patients reporting Above** (most common AE in trial drug 1)
24. **Tabulation of AE?** Quoted in both number and percentage/ percentage only/ number only/ No AE table
25. **Were AE in each arm mentioned?** Yes, each arm mentioned and quoted separately in both text of article and table/ Yes, each arm mentioned and quoted separately but only in the table/ Yes, mentioned but results are clumped together/ No data given.

Appendix J: Raw data for chapter nine.

Pregabalin in epilepsy and neuropathy trials

Outcome: Any Adverse Event				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
150mg		Two trials were evaluable	Three trials were evaluable	
300mg		One trial was evaluable	Two trials were evaluable	
600mg		Three trials were evaluable	Zero trials were evaluable	
Any dose		Two trials were evaluable	Seven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity epilepsy and neuropathy**
150mg	1.07 (0.86-1.34)	1.09 (1.33-3.44)	66%	44%
300mg	1.14 (0.99-1.32)	1.25 (0.98-1.59)	NA as one RCT	59%
600mg	NA	NA	NA	NA
Any dose	3.52 (2.48-5.00)	3.01 (2.40-3.78)	0%	27%

Outcome: Ataxia				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
150mg		Two trials were evaluable	Three trials were evaluable	
300mg		One trial was evaluable	Five trials were evaluable	
600mg		Four trials were evaluable	Six trials were evaluable	
Any dose		Three trials were evaluable	Seven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity epilepsy and neuropathy**
150mg	1.07 (0.86-1.34)	1.09 (1.33-3.44)	66%	44%
300mg	1.14 (0.99-1.32)	1.25 (0.98-1.59)	NA as one RCT	59%
600mg	NA	NA	NA	NA
Any dose	3.52 (2.48-5.00)	3.01 (2.40-3.78)	0%	27%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
150mg		Two trials were evaluable	Three trials were evaluable	
300mg		One trial was evaluable	Seven trials were evaluable	
600mg		Four trials were evaluable	Eleven trials were evaluable	
Any dose		Three trials were evaluable	Thirteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity epilepsy and neuropathy**
150mg	2.05 (1.18-3.57)	2.14 (1.33-3.44)	0%	0%
300mg	3.46 (1.73-6.93)	3.75 (2.82-4.97)	NA as one RCT	0%
600mg	4.52 (3.33-6.15)	4.48 (3.57-5.62)	0%	2%
Any dose	3.52 (2.48-5.00)	3.01 (2.40-3.78)	0%	27%

Outcome: Fatigue				
Dose	**Trial description (Epilepsy only)**		**Trial description (Epilepsy and Neuropathy)**	
Any dose	One trial was evaluable		Five trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	1.82 (0.53-6.27)	1.47 (1.00-2.16)	NA as one RCT	0%

Outcome: Headache				
Dose	**Trial description (Epilepsy only)**		**Trial description (Epilepsy and Neuropathy)**	
150mg	Two trials were evaluable		Five trials were evaluable	
300mg	One trial was evaluable		Five trials were evaluable	
600mg	Three trials were evaluable		Nine trials were evaluable	
Any dose	Four trials were evaluable		Fourteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
150mg	0.54 (0.29-1.00)	0.69 (0.44-1.08)	0%	0%
300mg	0.43 (0.16-1.15)	0.65 (0.43-0.97)	NA as one RCT	0%
600mg	0.78 (0.46-133)	0.87 (0.64-1.17)	0%	0%
Any dose	0.62 (0.43-0.89)	0.87 (0.66-1.15)	0%	56%

Outcome: Nausea Not reported in epilepsy trials

Outcome: Somnolence				
Dose	**Trial description (Epilepsy only)**		**Trial description (Epilepsy and Neuropathy)**	
150mg	Two trials were evaluable		Six trials were evaluable	
300mg	One trial was evaluable		Seven trials were evaluable	
600mg	Four trials were evaluable		Eleven trials were evaluable	
Any dose	Five trials were evaluable		Nineteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
150mg	1.29 (0.71-2.35)	1.73 (1.12-2.65)	0%	0%
300mg	1.62 (0.79-3.30)	3.38 (2.20-5.44)	NA as one RCT	24%
600mg	2.56 (1.82-3.61)	3.57 (2.61-4.88)	0%	21% trials are
Any dose	2.17 (1.58-2.99)	2.88 (2.25-3.68)	0%	30%

Outcome: Withdrawals due to AE				
Dose	**Trial description (Epilepsy only)**		**Trial description (Epilepsy and Neuropathy)**	
150mg	Two trials were evaluable		Six trials were evaluable	
300mg	One trial was evaluable		Seven trials were evaluable	
600mg	Four trials were evaluable		Eleven trials were evaluable	
Any dose	Three trials were evaluable		Fourteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**

150mg	0.78 (0.12-5.11)	1.29 (0.76-2.19)	64%	0%
300mg	2.89 (1.07-7.78)	2.37 (1.59-3.51)	NA as one RCT	15%
600mg	3.74 (2.44-5.73)	2.72 (2.11-3.49)	0%	6%
Any dose	3.11 (1.82-5.30)	2.19 (1.73-2.78)	0%	8%

Gabapentin in epilepsy and headache trials

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Five trials were evaluable	Seven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	1.27 (1.16-1.39)	1.37 (1.19 -1.59)	0%	54%

Outcome: Ataxia				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Three trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	(1.77-2.94)	2.07 (1.06 -4.04)	0%	29%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Six trials were evaluable	Eight trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	2.42 (1.63-3.59)	2.62 (1.86 -3.69)	0%	0%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Four trials were evaluable	Five trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	0.89 (0.53-1.48)	1.12 (0.61 -2.07)	0%	28%

Outcome: Somnolence		
Dose	**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**
Any dose	Six trials were evaluable	Eight trials were evaluable

Dose	RR Epilepsy only (95% CI)	RR Epilepsy and Headache	Statistical heterogeneity (I^2) epilepsy only	Statistical heterogeneity (I^2) epilepsy and headache
Any dose	2.28 (1.72-3.01)	2.29 (1.76 -3.00)	0%	0%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Three trials were evaluable	Five trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	1.39 (0.51-3.81)	1.65 (0.92-2.96)	22%	0%

Gabapentin in epilepsy and neuropathy trials

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Five trials were evaluable	Twelve trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.27 (1.16-1.39)	1.30 (1.30 -1.68)	0%	51%

Outcome: Ataxia				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Three trials were evaluable	Seven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.55 (0.76-8.54)	2.87 (1.35 -6.12)	51%	26%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Five trials were evaluable	Twelve trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.42 (1.63-3.59)	2.88 (2.31 -3.58)	0%	0%

Outcome: Fatigue				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Four trials were evaluable	Nine trials were evaluable	
Dose	**RR Epilepsy**	**RR Epilepsy and**	**Statistical**	**Statistical**

	only (95% CI)	Headache	heterogeneity (I^2) epilepsy only	heterogeneity (I^2) epilepsy and Neuropathy
Any dose	1.64 (0.96-2.81)	1.62 (1.01 -2.61)	0%	29%

Outcome: Headache				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Five trials were evaluable	Nine trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	0.73 (0.40-1.36)	1.12 (0.56 -2.20)	21%	43%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Four trials were evaluable	Thirteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	0.89 (0.53-1.48)	0.93 (0.68 -1.26)	0%	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Six trials were evaluable	Fourteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.14 (1.59-2.87)	2.59 (2.06 -3.25)	0%	1%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Four trials were evaluable	Fourteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.78 (0.84-3.77)	1.77 (1.31 -2.39)	17%	0%

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
200mg		One trial was evaluable	One trial was evaluable	
Any dose		Three trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Migraine**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
200 mg	0.57 (0.18-1.82)	1.71 (0.23-12.77)	NA	90%
Any dose	1.05 (0.91-1.20)	1.34 (1.11-1.61)	0%	80%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
200mg		One trial was evaluable	No headache trials were evaluable	
Any dose		four trials were evaluable	Eight trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Migraine**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	1.23 (0.82-1.85)	1.13 (0.83-1.54)	41%	30%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Eight trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Migraine**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	2.18 (0.52-9.20)	1.60 (1.15-2.23)	0%	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
200mg		One trial was evaluable	Two trials were evaluable	
Any dose		Seven trials were evaluable	eleven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Migraine**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
200 mg	3.11 (1.73-6.01)	3.31 (1.90-5.79)	NA	0%
Any dose	1.73 (1.22-2.47)	1.76 (1.33-2.33)	40%	18%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
200mg		One trial was evaluable	Three trials were evaluable	
Any dose		Ten trials were evaluable	Sixteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Migraine**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
200 mg	1.75 (0.55-5.57)	2.55 (0.70-9.28)	NA	90%
Any dose	2.03(1.12-3.67)	2.07 (1.44-2.98)	23%	24%

Topiramate in epilepsy and neuropathy trials

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Three trials were evaluable	One trial was evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	1.05 (0.91-1.22)	1.10 (0.99-1.21)	0%	0%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Seven trials were evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	1.35 (0.91-1.99)	1.31 (0.98-1.75)	37%	17%

Outcome: Headache				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Six trials were evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	0.85 (0.60-1.19)	0.84 (0.63-1.12)	46%	33%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	One trial was evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	2.18 (0.52-9.20)	1.84 (0.86-3.90)	0%	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	1.90 (1.44-2.50)	1.95 (1.53-2.48)	14%	0%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Neuropathy**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and neuropathy**
Any dose	1.96 (1.03-3.71)	1.94 (1.07-3.50)	3%	28%

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Four trials were evaluable	Nine trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.33 (0.95-1.856)	1.29 (1.05 – 1.57)	76%	60%

Outcome: Ataxia				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Eleven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.46 (1.11-5.45)	2.49 (1.22 – 5.07)	47%	34%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Eleven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.50 (1.56-4.02)	2.17 (1.44 – 3.29)	30%	33%

Outcome: Headache				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Eleven trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.22 (0.90-1.64)	1.18 (0.89– 1.56)	0%	0%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Six trials were evaluable	Ten trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.86 (1.22-2.83)	1.67 (1.17– 2.40)	0%	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Eight trials were evaluable	Twelve trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.65 (0.93-2.95)	1.64 (0.91– 2.96)	23%	58%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Six trials were evaluable	Fourteen trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	4.11 (1.49-11.35)	2.18 (1.37– 3.45)	0%	8%

Lamotrigine and headache trials

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Four trials were evaluable	Five trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	1.34 (1.14-1.57)	1.38 (1.18 – 1.62)	68%	64%

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Seven trials were evaluable	Eight trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	2.34 (1.71-3.19)	2.28 (1.69 – 3.07)	18%	7%

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Five trials were evaluable	Six trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	1.85 (1.20-2.85)	1.76 (1.15 – 2.69)	0%	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Eight trials were evaluable	Nine trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	1.65 (0.93-2.95)	1.73 (1.00 – 2.99)	23%	17%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Eight trials were evaluable	Nine trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and headache**
Any dose	5.09 (2.28-11.37)	4.47 (2.27 – 8.79)	0%	0%

Oxcarbazepine in epilepsy and neuropathy trials

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.36 (1.55-3.59)	3.03 (1.8-5.12)	8 %	50 %

Outcome: Fatigue				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.14 (1.21-3.76)	2.21 (1.37-3.57)	0 %	0 %

Outcome: Headache				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	1.13 (0.86-1.50)	1.46 (0.84-2.54)	0 %	58 %

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	2.86 (1.76-4.65)	2.93 (1.98- 4.34)	0 %	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	3.82 (0.67-21.83)	4.12 (1.38- 12.29)	49 %	51%

Outcome: Withdrawal due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		Two trials were evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	3.60 (1.55-8.38)	4.02 (2.73- 5.92)	28 %	0%

Oxcarbazpeine in epilepsy and headache trials

Outcome: Any AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	1.20 (1.11-1.31)	2.43 (1.02- 5.79)	0 %	96%

Outcome: Ataxia				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		One trials was evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	3.81 (1.97-7.37)	2.5 (1.95-6.61)	NA	0 %

Outcome: Dizziness				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	2.36 (1.55-3.59)	2.41 (1.7-3.41)	8 %	0 %

Outcome: Fatigue				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials was evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	2.14 (1.21-3.76)	2.32 (1.44-3.73)	0%	0 %

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	2.86 (1.76-4.65)	2.96 (1.91- 4.61)	0 %	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	3.82 (0.67-21.83)	2.12 (0.95-4.72)	49 %	43%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		Two trials were evaluable	Three trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	3.60 (1.55-8.38)	3.24 (1.71- 6.13)	28 %	25%

Valporate in epilepsy and headache trials

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		One trials was evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	3.51 (1.90-6.52)	2.74 (1.84-4.09)	NA	0%

Outcome: Somnolence				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Headache)**	
Any dose		One trials was evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	2.20 (1.03-4.69)	2.41 (1.35-4.31)	NA	0%

Outcome: Withdrawal due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		One trials was evaluable	Four trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Headache**
Any dose	4.40 (0.53-36.78)	2.0 (0.81-4.94)	NA	0%

Valproate in epilepsy and neuropathy trials

Outcome: Nausea				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		One trials was evaluable	Two trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	3.51 (1.90-6.52)	3.56 (1.95– 6.52)	NA	0%

Outcome: Withdrawals due to AE				
Dose		**Trial description (Epilepsy only)**	**Trial description (Epilepsy and Neuropathy)**	
Any dose		One trials was evaluable	Five trials were evaluable	
Dose	**RR Epilepsy only (95% CI)**	**RR Epilepsy and Headache**	**Statistical heterogeneity (I^2) epilepsy only**	**Statistical heterogeneity (I^2) epilepsy and Neuropathy**
Any dose	4.40 (0.53-36.78.)	2.96 (0.90– 9.70)	NA	0%

Appendix K: Submitted publications

Platform Presentations

June 2009 An Analysis of adverse event reporting of antiepileptic drugs: A systematic review
Association of British Neurologist meeting June 2009

June 2010 Reporting of Adverse events in Randomised Controlled Trials is poor and has not changed since publication of the CONSORT guidelines
European Congress in Epilepsy, Rhodes, Greece. 29th June 2010

Papers

November 2011 Reporting of adverse events in Randomised controlled trials of antiepileptic drugs using the CONSORT criteria for reporting harms.
Arif Shukralla, Catrin Tudur-Smith, Graham Powell, Paula Williamson, Anthony Marson
Epilepsy Research Vol 97 Issue (1-2), 20-29.

June 2015 Lacosamide add-on for refractory epilepsy.
Jenifer Weston, Arif Shukralla, Anthony Marson
Cochrane Database of Systemic Reviews 2015 Issue
DOI 10.1002/14651858.CD008841.pub2.

November 2016 Oxcarbazepine add-on for drug-resistant partial epilepsy
Sergio Castillo, Dieter Schmidt, Sarah White, Arif Shukralla
Cochrane Database of Systemic Reviews, 2009 Issue 3
DOI: 10.1002/14651858.CD002028.pub2

Posters/Abstracts

October 2009 Current reporting of adverse events in antiepileptic drug trials: A quantitative and qualitative analysis.
Arif Shukralla Anthony Marson
Epilepsia Vol 50 (Suppl 10) pg 107

August 2011 Adverse events of antiepileptic drugs, across indications: Can randomised controlled trial data from non-epilepsy indications be included in meta-analysis for AEDs used in epilepsy?
Arif Shukralla, Catrin Tudur-Smith, Anthony Marson
Epilepsia Vol 52(Suppl 6) pg 120

December 2011 Anti-epileptic drug harms: Issues for Meta-analysis
Catrin Tudur-Smith, Arif Shukralla, Sarah Donnegan, Anthony Marson
Trials vol 12 Suppl 1, A11

February 2012 Can randomised controlled trial data from non-epilepsy indications be included in meta-analysis for AEDs used in epilepsy? An analysis of adverse event data.
Arif Shukralla, Catrin Tudur-Smith, Anthony Marson
JNNP Feb 2012 Vol 83 Vol. 83 (pp. e1.220-e1).
DOI:10.1136/jnnp-2011-301993.96

Epilepsy Research (2011) **97**, 20—29

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Reporting of adverse events in randomised controlled trials of antiepileptic drugs using the CONSORT criteria for reporting harms

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KEYWORDS
Antiepileptic drugs;
CONSORT;
Reporting;
Harms;
Adverse events

Summary
Purpose: To assess the reporting of adverse events (AEs) in randomised controlled trials (RCTs) of antiepileptic drugs (AEDs) using the CONSORT statement for harms 2004, and to determine if reporting has changed since introduction of this standard.
Principal results: One hundred and fifty two RCTs were included from a search of papers published between 1999 and 2008 inclusive. We identified 23 criteria in the CONSORT statements. The mean number of criteria met per trial was 11.3 (95%CI 10.6—12.0). Commercially funded studies met 12.6 and non-commercially funded met 9.4 ($p < 0.001$). Trials recruiting adults met 12.5 and trials recruiting children met 9.3 ($p < 0.001$). Trials published before 2004 met 11.6 and trials published after 2004 met 11.1 ($p = 0.53$). Commercially funded trials met the majority of criteria more than non-commercially sponsored trials, particularly for definition of AEs (RR 3.15, CI 1.67—5.95) and the use of a validated dictionary of terms (RR 3.46, CI 1.41—8.44). Definitions for AEs (RR 2.32, CI 1.07—5.02) and details of analyses (RR 2.05, CI 1.01—4.15) were reported in adult trials more often than trials in children.
Major conclusions: Reporting of AEs in RCTs of AEDs is poor and has not improved since the publication of the CONSORT guidelines on the reporting of harms. Commercially funded trials were better reported than non-commercially funded trials

Abbreviations: AE, adverse event; TEAE, treatment emergent adverse event; SD, standard deviation; CI, confidence interval; AED, antiepileptic drug; RR, relative risk; RCT, randomised controlled trial; SAE, serious adverse event; CONSORT, consolidated standards of reporting trials.

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and trials recruiting adults were better reported than trials recruiting children. These findings have serious implications as poor reporting precludes bias being detected and hinders adequate risk benefit analyses. Journal editors, authors and reviewers should be encouraged to follow current guidance.

Introduction

Randomised controlled trials (RCTs) provide the best source of information about the effects of medical interventions. Consequently they have been pivotal in the emergence of evidence based medicine. The primary outcome in RCTs is usually a measure of benefit, with harms usually included as secondary outcomes. Treatment decisions often involve a consideration of benefits and harms. Therefore, to inform these decisions we need reliable evidence about potential harms, including the nature of the adverse events (AEs), their likelihood and severity.

Informed treatment decisions are important for chronic conditions such as epilepsy, where antiepileptic drug (AED) treatment might be taken for many years, and where the adverse events can have a significant effect on quality of life (Baker and Jacoby, 2000). Adverse events like memory disturbance, headaches and dizziness are common among people with epilepsy, and although they might arise during the conduct of a trial, they might not necessarily be caused by the trial treatment. The RCT provides a means of assessing whether such events are significantly associated with a specific treatment, either by comparison with placebo or with other treatments. RCTs can therefore provide estimates of incidence, duration and severity of adverse events as well as their causality. Adverse events investigated in RCTs include those that are common and often dose related, while in addition the overall impact of numerous AEs can be assessed by using adverse event scales (Baker et al., 1995), and risks vs. benefits can be assessed within measures of quality of life.

RCTs in isolation may not be the most appropriate research design to assess a number of important AEs. This is because RCTs are often not sufficiently powered to detect differences in AEs and patient populations are not representative of clinical practice. Therefore longer term observational studies are needed to discern AEs not seen in RCTs. Careful examination of such data eventually allows the distinction between AEs which may be associated with the prescription of a drug but are not directly attributable to it from adverse effects which are attributable to the drug.

Adverse event is therefore a broad term to encompass both expected and clinically plausible consequences of drugs and unexpected occurrences. Adverse effects of drugs or adverse drug reactions are those occurrences that are directly and clinically attributable to a drug.

Given the importance of RCTs, it is especially important that when they are reported in medical journals, sufficient and appropriate details regarding both benefits and harms are provided in the report. Concerns about the quality of reporting of RCTs has already been highlighted and as a result guidance on reporting has been produced by the CONSORT group, which constitutes a number of leading medical journal editors and academics (Altman, 1996).

Many journals now require authors to report RCTs according to the CONSORT guidelines, although at the time of writing the CONSORT guidelines are not actively endorsed by the journal Epilepsy Research or other subspecialty journals. The CONSORT guidance gives recommendations on the reporting of methods, outcomes, analyses and results (Altman et al., 2001), and more recently the guidance has been updated to provide specific and comprehensive recommendations on AE reporting (Ioannidis et al., 2004).

In this paper we assess the reporting of adverse events in RCTs of AEDs published over the last decade against the standards set out in the CONSORT guidelines, highlight inadequacies and make recommendations for improving reporting.

Methods

Aims

The primary aim was to assess the quality of reporting of AEs in RCTs using the extended CONSORT statement for harms. Secondary aims were to compare the quality of trials (i) funded by industry vs. those not funded by industry, (ii) trials recruiting adults vs. those recruiting children, (iii) trials published before and after the publication of the amended CONSORT guidelines of 2004 and (iv) trials published in epilepsy journals vs. those published in non-epilepsy journals.

Eligibility and identification of studies

We searched for citations using MEDLINE, Cochrane Library and the Epilepsy Group trials register for trials published between January 1999 and December 2008 inclusive. Search terms used in electronic databases were ''epilepsy'', ''antiepileptic drug'' and ''seizure''.

Inclusion criteria for studies were: RCTs comparing AEDs; RCT patient population with epilepsy; RCTs published in English. Trials were assessed for inclusion by reading the abstract and, if necessary, the full report.

Exclusion criteria for studies were: RCTs assessing surgical interventions and vagus nerve stimulation; RCTs where neuropsychological outcomes were the primary outcome since these were secondary reports of studies where the primary report has included data on seizures and AEs.

In order to assess the reliability of this selection process, two authors (A.S. and G.P.) independently assessed for inclusion studies published in 2007. If there was good agreement for this subset of trials we planned for one author (A.S.) to assess the remainder of studies for inclusion.

Data collected: items from CONSORT criteria and scoring

The CONSORT criteria make ten recommendations for reporting harms (Ioannidis et al., 2004). These provide guidelines for each section of an RCT report from the title to the discussion. Some of these recommendations include more than one item of information. Two authors (A.S. and G.P.) compiled a checklist of items for data extraction based upon the CONSORT statements which were then

Table 1 CONSORT recommendations and data items collected (modified from Ioannidis et al. (2004)).

Section of paper	CONSORT recommendations	Descriptor of CONSORT recommendations pertaining to adverse events	Checklist of data collected
Title & abstract	1	If the study collected data on harms and benefits, the title or abstract should so state	1. Adverse events (AEs) mentioned in title or abstract
Introduction	2	If the trial addresses both harms and benefits, the introduction should so state	2. Information on AEs mentioned in introduction
Methods	3	List addresses adverse events with definitions for each (with attention, when relevant to grading expected vs. unexpected events, reference to standardised and validated definitions and descriptions of new definitions)	3. If definition of AE mentioned 4. If article mentioned all or selected sample of AE 5. If article mentions treatment emergent adverse events (TEAEs) 6. If article mentions use of a validated instrument to report AEs 7. If dictionaries for coding of AEs mentioned
	4	Clarify how harms related information is collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms related monitoring and stopping rules if pertinent)	8. Description of how harms data were collected e.g. diaries, phone interviews or face to face interviews 9. Description of when AE data were collected 10. Description of how AE were attributed to trial drugs
	5	Describe any plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures and any statistical analysis)	11. Description of methods for presenting and analysing AEs methods section 12. Description of approach for the handling of recurrent AEs
Results	6	Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment	13. Description of withdrawals due to AEs in each arm 14. If article contains data on serious adverse events and death
	7	Provides denominators for describing harms	15. Provide denominators for AEs 16. Provide definitions used for analysis set (Trials may use either intention to treat or safety population as the analysis set for harms data. If trials explicitly mentions which of these were used, then this item is met. This is not to be confused with item 3) 17. If trial states same analysis set used for efficacy and safety
	8	Present the absolute risk of each adverse event (specifying type, grade and seriousness per arm) and present appropriate metrics for recurrent events, continuous variables and scale variables whenever pertinent	18. Results presented separately for each treatment arm 19. Severity and grading of AEs 20. Provide both number of AEs and number of patients with AEs
	9	Describe any subgroup analysis and exploratory analysis for harms	Data not collected as very few trials conduct subgroup analysis
Discussion	10	Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability and other sources of information on harms	21. If prior literature is cited in the discussion in relation to adverse events 22. If the discussion is balanced with regards to efficacy and AEs 23. If limitations of the study are discussed

discussed among the wider review team. The completed checklist included twenty-three items that were most relevant to epilepsy trials, which are summarised in Table 1.

We excluded CONSORT recommendation nine (*describe any subgroup analyses and exploratory analyses for harms*) because very few trials carry out subgroup analysis on efficacy criteria, and such analyses in AE outcomes would be rarer still and it would be unrealistic for papers to report subgroups for harm data. For each item a score of one point was awarded. The minimum possible overall score was zero and the maximum was twenty-three.

Information about study funding (commercially vs. non-commercially funded studies) was taken from the text of the article, including acknowledgements. Those that did not mention sources of funding were classified as non-commercially funded trials. We extracted participant ages from trial reports. We defined a child as any person less than or equal to 12 years of age. Trials were categorised into those recruiting adults only, trials recruiting children only and trials with mixed populations.

Data extraction

We designed data collection forms to extract data pertaining to the twenty three items. Data extraction was carried out independently by two authors (A.S. and G.P.) from a random sample of fourteen trial reports. Results were compared to determine inter-rater reliability. Any disagreements were clarified by mutual discussion. If data extraction was deemed reliable, then the data for remaining trials were to be extracted by one author (AS) with any further difficulties resolved by discussion.

Data analysis

Inter-rater agreement of extracted data was assessed by calculating Cohen's kappa statistic and 95% confidence interval (Cohen, 1968). We calculated the mean number of items met for each trial and each subgroup within each trial. Between group comparisons were made using un-paired *t*-tests. The proportion of trials reporting each item was calculated for the whole trial population and among the subgroups of interest. Relative risks and 95% confidence intervals were used to summarise comparative effects. Analyses were carried out using SPSS (Version 17.0) using a two-sided significance level of 5%.

Results

Trial disposition and inclusion

Two hundred and fifty seven trials that were published in 2007 were assessed for eligibility by both AS and GP. One author selected 13 articles, while the second author selected the same 13 articles plus one additional article. This additional article was excluded by mutual agreement and we concluded that the assessment of study eligibility was reproducible; the remainder of studies were assessed by one author (A.S.). Our search of bibliographic databases identified 2052 citations, of which 152 trial reports met our inclusion criteria (Fig. 1).

Inter-rater agreement for data extraction

Overall there was good agreement between the two authors (A.S. and G.P.) in data extraction from studies published in 2007. The authors, however, differed in the interpretation of CONSORT recommendation number three (checklist item four) for the reporting of all or selected sample of AEs. After further discussion all 152 trials were re-assessed for this item by both authors and results compared again. Following the re-assessment of item three the overall agreement across all items was good with a kappa value of 0.78 (95%CI of 0.64—0.92). Data extraction for remaining trials was carried out by one author (AS) as data extraction was deemed to be reliable.

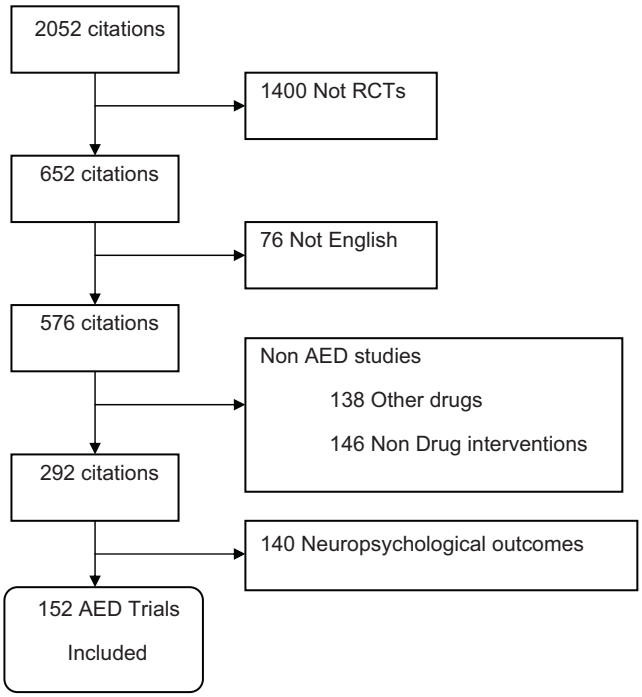

Fig. 1 Selection of studies.

Characteristics of studies

We included 152 trials published between 1999 and 2008 (Table 2). These randomised a total of 30,650 patients with a median number recruited per trial of 135 patients (range of 16—1721 patients). Sixty two percent of trials were commercially funded and 38% were non-commercially funded. Seventy nine percent were double blinded, 3% single blinded and 18% unblinded. Fifty two percent of studies recruited only adults, 25% recruited both adults and children and 23% of studies recruited only children. Eighty three percent of trials were multicentre and 17% were single centre studies.

Trial reports detailed various AEDs as interventions, the most common being topiramate (14%), levetiracetam (13%) and lamotrigine (13%). Forty nine percent of trials were placebo controlled and 51% of trials were actively controlled. Forty eight percent were published in epilepsy journals and the remainder in general neurology journals.

Results for all studies

Across all 152 included studies the mean number of items met per study was 11.3 (95%CI 10.6—12.0); the minimum was zero and the maximum was 21. None of the trials met all 23 items (Table 3). There was considerable variation in

Table 2 Characteristics of included studies.

		Number of trials (%) total = 152
Demographics	Adults	79 (52)
	Children (age <12 years)	35 (23)
	Both adults and children	38 (25)
Blinding	Double blinded	120 (79)
	Single blinded	4 (3)
	Open label	28 (18)
Epilepsy type in population	Focal epilepsy	102 (67)
	Generalised epilepsy	8 (5)
	Both focal and generalised epilepsy	42 (28)
Funding	Commercially funded	94 (62)
	Non-commercially funded	58 (38)
Centre	Multi-centre	126 (83)
	Single-centre	26 (17)
Intervention	Placebo controlled	75 (49)
	Actively controlled	77 (51)
Journal type	Epilepsy journal	75 (49)
	Non-epilepsy journal	77 (51)
Median duration of trial (weeks)	28 weeks (range 4—294)	

the percentage of trial reports meeting individual criteria (Table 4) ranging from 7.2% of trials reporting recurrent adverse events to 87.5% of trials reporting harms in the title or abstract. The single trial that scored zero did not include any data relating to harms and the content was focused on recording number of seizures as its primary outcome (Wang et al., 2001).

The CONSORT criteria require the reporting of harms in either the title or abstract. Our results indicate that 87.5% of trials do this and this was the most commonly met item. Other items that were frequently satisfied were; the reporting of denominators for AEs (78.3% of trials), the timing of AEs (76.3% of trials), the mention of harms in the introduction (74.3% of trials), the reporting of serious adverse events (SAEs) or death (72.3% of trials) and withdrawals due to AEs (71.0% of trials). Items that were not frequently reported were; use of a validated dictionary (21.7% of trials), use of a validated instrument (15.8% of trials), reporting of both number of AEs and number of patients with AEs (19.1% of trials) and handling of recurrent events (7.2% of trials). Table 4 provides further details.

Commercially vs. non-commercially funded studies

Significantly more items were reported in commercially funded studies than non-commercially funded studies (mean items 12.6 and 9.4 respectively) with difference in means of 3.2 (95%CI: 1.8—4.5), $p < 0.001$ (Table 3). All criteria, except the mention of harms in the introduction, were met more

Table 3 Comparison of means of CONSORT scores.

	Number of trials	Mean CONSORT items met	Range of items	Difference in means	95% CI for difference of means	*P* Value
Commercially funded	94	12.6	1—21			
Non-commercially funded	58	9.4	0—17	3.2	1.8 to 4.5	<0.001
Pre CONSORT	86	11.6	0—19			
Post CONSORT	66	11.1	3—21	0.5	−0.9 to 1.8	0.529
Adults	79	12.5	3—21			
Children (excluded 38 trial recruiting adults and children)	35	9.3	3—16	3.2	1.6 to 4.7	<0.001
Epilepsy journal	75	11.4	0—22	0.0	NA	NA
Non-epilepsy journal	77	11.4	3—19			

Table 4 Relative risks of trial subgroups meeting individual items and percentage of trials meeting individual items.

CONSORT item	Item	Relative risk of commercially vs. non-commercially funded trials (95%CI)	Relative risk of adult trials vs. children (95%CI)	Relative risk of Post CONSORT trials vs. pre CONSORT (95%CI)	Relative risk of epilepsy journal vs. non-epilepsy journal (95%CI)	Percentage of total number of trials meeting item (%)
Harms in title or abstract	1	1.09 (0.96–1.25)	1.09 (0.91–1.31)	1.01 (0.89–1.14)	1.04 (0.94–1.16)	87 .5
Harms in introduction	2	0.93 (0.77–1.12)	1.13 (0.88–1.45)	1.11 (0.92–1.34)	1.04 (0.87– 1.26)	74 .3
Definition of AE	3	3.15 (1.67–5.95)	2.32 (1.07–5.02)	0.63 (0.40–1.01)	1.15 (0.75– 1.75)	36 .2
All or selected sample	4	2.34 (1.27–4.34)	1.44 (0.73–2.84)	1.10 (0.69–1.76)	1.12 (0.70– 1.78)	31 .6
Treatment Emergent AE	5	1.69 (1.12–2.55)	1.33 (0.79–2.21)	1.34 (0.96–1.88)	1.12 (0.80–1.57)	46 .7
Validated instrument	6	1.23 (0.56–2.70)	1.39 (0.49–3.94)	1.10 (0.53–2.30)	1.21 (0.58– 2.54)	15 .8
Validated dictionary	7	3.46 (1.41–8.44)	1.67 (0.68–4.08)	0.35 (0.16–0.76)	1.23 (0.67– 2.26)	21 .7
Mode of AE collection	8	1.09 (0.82–1.47)	1.32 (0.88–1.96)	0.94 (0.71–1.25)	0.98 (0.74– 1.29)	56 .6
Timing of AE	9	1.01 (0.84–1.21)	1.18 (0.90–1.53)	0.95 (0.79–1.14)	0.99 (0.83– 1.18)	76 .3
Details of attribution	10	1.85 (1.08–3.16)	1.27 (0.70–2.30)	1.30 (0.84–2.02)	0.88 (0.57–1.37)	33 .3
Details of presentation and analysis	11	1.05 (0.67–1.64)	2.05 (1.01–4.15)	0.83 (0.53–1.29)	0.71 (0.45–1.10)	35 .5
Handling of recurrent AE	12	2.78 (0.62–12.40)	1.59 (0.36–7.12)	0.29 (0.06–1.30)	1.23 (0.39–3.87)	7 .2

Table 4 (*Continued*)

CONSORT item	Item	Relative risk of commercially vs. non-commercially funded trials (95%CI)	Relative risk of adult trials vs. children (95%CI)	Relative risk of Post CONSORT trials vs. pre CONSORT (95%CI)	Relative risk of epilepsy journal vs. non-epilepsy journal (95%CI)	Percentage of total number of trials meeting item (%)
Early or late withdrawals	13	1.09 (0.88–1.36)	1.66 (1.16–2.37)	0.80 (0.64–1.30)	0.79 (0.64–0.97)	71 .0
Serious AEs or death	14	1.27 (1.01–1.59)	0.99 (0.79–1.25)	1.11 (0.97–1.28)	0.99 (0.81–1.21)	72 .3
Provide denominators for AEs	15	1.17 (0.97–1.42)	1.23 (0.95–1.59)	0.96 (0.80–1.14)	1.01 (0.85–1.19)	78 .3
Provide definitions used for analysis set	16	2.07 (1.26–3.41)	1.77 (0.96–3.25)	0.90 (0.61–1.35)	0.99 (0.67–1.47)	40 .1
Same analysis set used for efficacy and safety	17	2.04 (1.09–3.81)	1.53 (0.74–3.19)	0.94 (0.56–1.57)	0.98 (0.59–1.63)	34 .9
Results presented separately	18	1.45 (1.12–1.89)	1.80 (1.21–2.69)	0.99 (0.80– 1.24)	1.11 (0.89–1.38)	68 .4
Severity and grading of AEs	19	1.50 (1.02–2.21)	0.88 (0.60–1.31)	0.83 (0.59–1.18)	0.73 (0.52–1.03)	47 .3
Provide both number of AEs and number of patients with AEs	20	1.62 (0.77–3.41)	2.09 (0.77–5.65)	1.22 (0.63–2.34)	0.63 (0.32–1.24)	19 .1
Discusses prior AE data	21	1.25 (0.98–1.60)	0.91 (0.70–1.18)	1.14 (0.92–1.41)	1.13 (0.91–1.41)	67 .8
Discussion is balanced	22	1.51 (1.11–2.05)	1.13 (0.82–1.57)	1.07 (0.83–1.38)	1.10 (0.85– 1.41)	61 .2
Discusses limitations	23	1.20 (0.8–1.82)	1.10 (0.67–1.81)	0.94 (0.64–1.39)	1.03 (0.70–1.51)	40 .8

frequently in reports of commercially funded trials with 95% confidence intervals (for the risk ratio comparing funding subgroups) excluding unity for 11 of the 23 criteria (Table 4).

Items with significant risk differences between commercially and non-commercially funded studies were; use of a validated dictionary (RR 3.46, CI 1.41—8.44), reporting a definition of AE (RR 3.15, CI 1.67—5.95), mention if all or selected sample of AE were reported (RR 2.34, CI 1.27—4.34). Providing a definition for the analysis set (RR 2.07, CI 1.26—3.41) and reporting if the same analysis sets were used for efficacy and safety (RR 2.04, CI 1.09—3.81) were also reported more frequently in commercially funded studies. Commercially funded trials reported a balanced account of efficacy and safety in discussion section better compared to non-commercially funded studies (RR 1.50, CI 1.02—2.21).

Pre vs. post CONSORT

We found no difference in the mean number of items met in studies reported before or after the publication of the CONSORT guidelines (mean items met 11.6 and 11.1 respectively) with difference in means of 0.6 (95%CI −0.9 to 1.8) (Table 3). For individual items the relative risk estimates were greater than one for some items and less than one for others with unity included within all of the 95%CIs except the reporting of a validated dictionary (RR 0.35, CI 0.16—0.76).

Adults vs. children

This analysis included 35 trials recruiting only children, and 79 studies recruiting only adults, while 38 trials recruiting both adults and children were not examined. Trials recruiting adults met significantly more criteria than those recruiting children (mean items met 12.5 and 9.3 respectively) with a difference in means of 3.2 (95%CI 1.6—4.7) (Table 3). Items that were met more frequently in adult trials were definition of AE (RR 2.32, CI 1.07—5.02), details of presentation and statistical analysis (RR 2.05, CI 1.01—4.15), results presented separately for each treatment arm (RR 1.80, CI 1.21—2.69) and reporting of early or late withdrawals (RR 1.66, CI 1.16—2.37).

Epilepsy vs. non-epilepsy journals

This analysis included 75 trials published in epilepsy journals and 77 in non-epilepsy journals. Trials published in both types of journals met 11.4 mean items. For individual items the relative risk estimates were not significantly different between the two groups except for reporting of early or late withdrawals (RR 0.79, CI 0.64—0.97).

Specific CONSORT items

A definition of what constitutes an AE was reported in 36.6% of trial reports. Commercially funded trials were more likely to report this than non-commercially funded trials (RR 3.15, CI 1.67—5.95), as were trials recruiting adults compared to trials recruiting children (RR 2.32, CI 1.07—5.02). Treatment emergent adverse events (TEAEs) are summaries for AEs that have either arisen *de novo* or increased from baseline following treatment. This was reported in 46.7% of trials and was more likely to be reported in commercially funded trials compared to non-commercially funded trials (RR 1.69, CI 1.12—2.55).

Withdrawals due to AEs is a useful measure of tolerability. Our analysis showed that this was reported in 71% of all trials. There were no differences between the subgroups for reporting of withdrawal data. Serious adverse events including death was also reported well with 72.3% of trials in our analysis. Commercially funded trials were better at this than non-commercially funded trials (RR 1.27, CI 1.10—1.59).

Reporting of both number of AEs and number of patients with AEs is poor in epilepsy trials, with only 19.1% of studies citing this data. However studies would instead report either absolute numbers of events or numbers of patients with events. Severity and grading of AEs was reported in nearly half of studies (47.3%), and this was more likely to be reported in commercially funded studies compared to non-commercially funded studies (RR 1.50, CI 1.02—2.21).

Discussion

Accurate knowledge about the risks and seriousness of AEs is required to inform treatment decisions; particularly for long term conditions such as epilepsy where there are multiple treatment alternatives and where treatment decisions often involve a consideration of benefit and harms. It is vitally important therefore that data about AEs are reliably provided in reports of RCTs.

This is the first study carried out in this therapeutic area, although similar work has been carried out in other areas (Smith et al., 2008; Chowers et al., 2009; Breau et al., 2010).

We have demonstrated that adherence to the 2004 CONSORT guidelines for reporting harms is poor in RCTs of AEDs. None of the trials met all 23 items. We also demonstrated that reporting is heterogeneous with some items reported more poorly than others. Such heterogeneity has also been demonstrated in previous work (Smith et al., 2008). We speculate that this heterogeneity might suggest either a lack of awareness of the guidelines or indicate bias in reporting some items. The CONSORT guidelines recommend adequate space be given to the reporting of harms. Bias in reporting could be related to the length of journal space available for harms data and much of this data is collected for regulatory authorities and not reported. Authors and journal editors should take necessary steps to summarise sufficient harms related information required by the CONSORT guidelines. There has been a trebling of supplementary content published online in recent years (Schringer et al., 2007) which would allow an alternate area for harms data to be published.

Our report also suggests that the quality of reporting of harms has not changed since publication of the 2004 guidelines. However, this might be because there are only small differences that could not be detected, or could also be accounted for by the fact that many of the journals do not endorse the CONSORT guidelines.

The initial CONSORT statement was published in 2001 and made recommendations for all areas of RCT reporting, but made only limited comments on AEs. Studies assessing

changes to RCT reporting according to the 2001 CONSORT guidance indicate that reporting of RCTs has improved since the 2001 guidance was published (Plint et al., 2006; Han et al., 2009). Thus although the reporting of RCTs has improved in general, our results indicate that the reporting of harms has not improved. We do accept that an editorial time lag would impact implementation of the CONSORT guidelines even for trials published after 2006, but our research indicates the need for better dissemination and implementation strategies for the CONSORT statement for harms.

Reporting of harms in the title and abstract of RCTs of AEDs is well adhered to, and this implies that data for harms will be accurately indexed in databases such as MEDLINE, making it possible to accurately mine for data regarding harms in published trials (Hopewell et al., 2008).

Recurrent AEs in the same patient are made explicit in trials by reporting both numbers of patients and number of events, our results show that this was very poorly reported; the definitions of AE data (use of a validated dictionary and use of a validated instrument) were also poorly reported. Some readers of published studies might incorrectly assume that the reporting of AEs would be to agreed terminology. This could be aided by the use of dictionaries with defined terms and the use of validated instruments to record AEs. We found poor reporting as to whether such instruments were used. Similarly we found that only 36% of trials mentioned the definition of adverse events and 56% of trials mentioned mode of AE collection. This makes the interpretation of data and making comparisons of data among trials very difficult.

Reporting of withdrawal data and SAEs is good in epilepsy trials, this is important as withdrawals data is comparable across studies and is a useful measure of tolerability. However poor reporting of both the number of events and number of patients with AEs makes it difficult for the reader to appreciate the true likelihood of a given AE.

Clinicians make judgments of reported AEs based not only on frequency or likelihood but also on severity. Many AEs reported in RCTs are mild and often dose related, however our report suggested that only half of epilepsy trials gave some indication of severity.

Commercially funded studies adhered to the guidelines better than non-commercially funded studies. Differences were found in almost all of the 23 items assessed with varying proportions in each item. The reason for this discrepancy is not clear but we suspect could be due to greater resource available for commercially funded trials, and greater experience in the preparation of detailed safety reports for regulatory authorities such as the European Medicines Authority and the Food and Drug Administration. Also use of validated dictionaries such as Medical Dictionary for Regulated Activities (MedDRA) is expensive and may be prohibitive for non-commercially funded trials. To address this issue, non-commercial investigators could create a dictionary similar to MedDRA for use in studies. Ideally such dictionaries should be made available for use internationally. If any dictionary is used then this should be stated in the trial report as recommended by CONSORT.

A recent meta-analysis showed significant improvement in quality of reporting when the CONSORT checklist is used and this differs between CONSORT adopters vs. non-adopters (Plint et al., 2006). It has been shown consistently that use of the CONSORT guidelines has improved reporting in a number of studies (Plint et al., 2006; Han et al., 2009) but these did not evaluate the extension guidelines for harms.

Reporting of AEs did not differ when comparing epilepsy and non-epilepsy journals, this is significant because none of the epilepsy specific journals have adopted the CONSORT guidelines whereas many of the general neurology journals have. The apparent lack of difference may also be due to the editorial time lag in adopting the guidelines, hence further work needs to be done to see if trials published in CONSORT endorsing journals have improved from 2006 onwards.

Children comprise a special group in which to carry out RCTs and trials in children can pose additional ethical challenges; nonetheless reliable data about harm in children is required. Our findings suggest that trials recruiting children reported AEs more poorly than trials in adults.

Our study was limited by the potential for subjective interpretation of the CONSORT criteria for harms. These criteria were open to individual interpretation and they differed from previous publications by the CONSORT group as a comprehensive checklist was not included. We limited bias in our analysis by using double data extraction methods and a wider review team carried out interpretation of the guidelines.

Recommendations

Reporting of AEs in RCTs is an important issue that needs to improve to allow judgements to be made between benefits and harms. We recognise that journals have limited space for the reporting of all outcomes and this can lead to selective outcome reporting. However we recommend that wherever possible authors allow adequate space for this. We would recommend firstly that subspecialty epilepsy journals endorse the CONSORT statements. We would recommend that journal editors should provide links to the CONSORT statements on their websites and refer to them in their instructions to authors. At the peer review stage we recommend that referees should comment on adherence to the guidance. We would also recommend that the CONSORT extension for harms is comprehensively incorporated in future updates as a checklist, making it easy for all stakeholders to follow so that proper evaluation can be made of the value of such a checklist, with the aim of improving quality of reporting AEs in the future.

Conflict of interest

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Oxcarbazepine add-on for drug-resistant partial epilepsy (Review)

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[Intervention Review]

Oxcarbazepine add-on for drug-resistant partial epilepsy

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ABSTRACT

Background

Most people with epilepsy have a good prognosis and their seizures can be well controlled with the use of a single antiepileptic drug, but up to 30% develop refractory epilepsy, especially those with partial seizures. In this review we summarize the current evidence regarding oxcarbazepine when used as an add-on treatment for drug-resistant partial epilepsy.

Objectives

To evaluate the effects of oxcarbazepine when used as an add-on treatment for drug-resistant partial epilepsy.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (21 May 2012), the Cochrane Central Register of Controlled Trials (CENTRAL Issue 5 of 12, *The Cochrane Library* 2012), MEDLINE (1946 to May week 2, 2012). No language restrictions were imposed. We checked the reference lists of retrieved studies for additional reports of relevant studies. We also contacted Novartis (manufacturers of oxcarbazepine) and experts in the field.

Selection criteria

Randomized, double-blinded, add-on trials of oxcarbazepine in patients with drug-resistant partial epilepsy.

Data collection and analysis

Two review authors independently assessed trials for inclusion and extracted the relevant data. For the update of this review, authors (AS) and (AM) used published data of trials included in the previous review and searched for new or previously missed studies. The following outcomes were assessed : (a) 50% or greater reduction in seizure frequency; (b) treatment withdrawal (any reason); (c) adverse events. Primary analyses were intention-to-treat. Summary relative risk ratios were estimated for each outcome.

Main results

Four trials were included representing 1128 randomised patients. Two trials comparing oxcarbazepine to placebo recruited 961 patients and the other two trails comparing two dosages of oxcarbazepine recruited 167 patients.

The overall relative risk for a 50% or greater reduction in seizure frequency compared to placebo was 2.51 (CI 1.89-3.34). The overall relative risk for treatment withdrawal compared to placebo was 1.72 (CI 1.36- 2.19). The overall relative risks for efficacy and tolerability

outcomes comparing high versus low dose could not be summarised in a meta analysis owing to differences in dosages used in the studies.

Authors' conclusions

Oxcarbazepine has efficacy as an add-on treatment in patients with drug-resistant partial epilepsy, both in adults and children. However, trials reviewed were of relatively short duration, and provide no evidence about the long-term effects of oxcarbazepine. Results cannot be extrapolated to monotherapy or to patients with other epilepsy types.

PLAIN LANGUAGE SUMMARY

Oxcarbazepine add-on for drug-resistant partial epilepsy

Oxcarbazepine is effective as a short-term combination treatment for partial epilepsy.

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Oxcarbazepine is an antiepileptic drug which can be used as an add-on treatment for people with drug-resistant partial epilepsy who are resistant to other antiepileptic drugs. The review of trials found that oxcarbazepine used in this way can reduce seizure frequency in the short-term for adults and children. The review did not include people with generalized epilepsy or look at the long-term effects of oxcarbazepine.

BACKGROUND

Epilepsy is one of the most disabling neurological disorders.Epilepsy predisposes patients to seizures which can lead to physical and psychosocial consequences. These would include depression, social stigma and implications for driving. Epilepsy is commonly treated with antiepileptic drugs with many patients rendered seizure free. (Kwan 2000) With the introduction of several new AEDs, there is a need for systematic reviews of these drugs, which will provide a resource for informing clinical practice (Marson 1997; Privitera 1999). New AEDs have been tested and used mainly as add-on therapies, adding them to standard drugs such as phenytoin, carbamazepine and valproate. The majority of trials investigating add-on therapy with AEDs have recruited patients with partial epilepsy (experiencing simple partial and/or complex partial and/or secondary generalized tonic-clonic seizures (Commission 1989)) that have been resistant to antiepileptic drug treatment. In this review, we focus upon the effect of oxcarbazepine when used as an add-on treatment for patients with drug-resistant partial epilepsy.

Oxcarbazepine is an analogue of its parent compound carbamazepine, which is a well established treatment for epilepsy. Oxcarbazepine is thought to have certain advantages over carbamazepine. In particular, the dose can be titrated to a therapeutic dose more quickly, (Grant 1992). In this review we focus upon oxcarbazepine's effect on seizures, side effects, cognition and quality of life.

OBJECTIVES

To assess the effects of oxcarbazepine when used as an add-on treatment for patients with drug-resistant partial epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review studies needed to meet all of the following criteria:
(1) randomised controlled trials, in which a concealed mechanism of randomisation was used (e.g. allocation of sequentially sealed packages of medication, sealed opaque envelopes);
(2) double, single or unblinded trials;
(3) placebo controlled or actively controlled studies;
(4) add-on studies;
(5) parallel group or cross-over studies. For cross-over studies, we planned to use the first treatment period as a parallel trial.

Types of participants

Patients of any age with drug-resistant partial epilepsy.
Seizures will be considered drug-resistant if they continue despite trying monotherapy with at least two of the standard antiepileptic drugs.

Types of interventions

(1) The active treatment group received therapy with oxcarbazepine in addition to their usual treatment.
(2) The control group received either placebo in addition to their usual treatment, or received a low dose of oxcarbazepine in addition to their usual treatment.

Types of outcome measures

(1) Fifty percent or greater reduction in seizure frequency
The proportion of patients with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomization baseline period was chosen as the primary outcome. It was chosen because it is commonly reported in this type of study, and can be calculated for studies that do not report it, provided that baseline seizure data were recorded.
(2) Treatment withdrawal
The proportion of patients having treatment withdrawn during the course of the treatment period was chosen as a measure of 'global measure of tolerability'. In studies of relatively short duration, treatment is unlikely to be withdrawn due to lack of efficacy, and any treatment withdrawal is likely due to side effects.
(3) Side effects
The proportion of patients experiencing any of the following side effects:

1. Ataxia
2. Dizziness
3. Fatigue
4. Nausea
5. Somnolence
6. Headache
7. Hyponatraemia
8. Vertigo
9. Diplopia
10. Rash
11. Tremor
12. Pyrexia
13. Abnormal gait
14. Abdominal pain
15. Nystagmus
16. Viral infection
17. Vomiting
18. Abnormal vision
19. Any Adverse Event

(4) Cognitive effects
At present, there is no consensus as to which instruments should be used to assess the effects of AEDs on cognition, and as a result the assessment of cognitive effects has been approached in a heterogeneous way (Cochrane 1998). In view of this difficulty, we planned to tabulate the results, but make no attempt to combine results in a meta-analysis.
(5) Quality of life
Once again, there is no consensus as to which instruments should be used to assess this, and quality of life data was summarized qualitatively.

Search methods for identification of studies

We searched the Cochrane Epilepsy Group's Specialized Register (21 May 2012) using the search term 'oxcarbazepine or trileptal'. This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant reports are also identified by handsearching selected journals and conference proceedings.
In addition, we carried out searching as follows:
Electronic databases
We searched the following databases. There were no language restrictions.
(1) The Cochrane Central Register of Controlled Trials (CENTRAL Issue 5 of 12, *The Cochrane Library* 2012) using the strategy set out in Appendix 1.
(2) MEDLINE (Ovid, 1946 to May week 2, 2012) using the search strategy set out in Appendix 2.
References from published studies
We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Efforts to identify unpublished studies
Unpublished data were sought from Novartis (manufacturers of oxcarbazepine). Following previous publication of this review unpublished studies were compared to corresponding published reports for variation in data. If minor variations were found, author used data from published studies only.
Other
We asked colleagues if they were aware of any studies which we may have missed.

Data collection and analysis

Two review authors (SC and DS) independently assessed trials for inclusion. Any disagreements were resolved by mutual discussion. For purposes of the update, two authors (AS and AM) searched for additional trials published after the year 2000 onwards, any additional studies were included in the update of this review by mutual agreement.

The same review authors extracted the following information from included trials (again, any disagreements were resolved by mutual discussion).

Methodological trial design

(a) Method of concealed randomisation.
(b) Method of blinding.
(c) Whether any patients had been excluded from reported analyses.
(d) Duration of baseline period.
(e) Duration of treatment period.
(f) Dose(s) of oxcarbazepine tested.

Patient/demographic information

(a) Number of patients allocated to each treatment group.
(b) Age/sex.
(c) Seizure types.
(d) Seizure frequency during baseline period.
(e) Number of background drugs.

Where necessary, original authors were asked to confirm the following:

(a) the method of randomisation;
(b) the total number of patients randomised in each group;
(c) the number of patients in each group achieving a 50% or greater reduction in seizure frequency per treatment group;
(d) the number of patients having treatment withdrawn post randomisation per treatment group.

For those excluded:

(a) the reason for exclusion;
(b) whether any of those excluded completed the treatment phase;
(c) whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Outcomes

The number of patients experiencing each outcome (*see* types of outcomes) were recorded per randomized group.

Analysis

(1) Fifty percent reduction in seizure frequency and treatment withdrawal

Clinical heterogeneity was assessed by comparing the distribution of several patient factors among included trials (age, predominant seizure type, duration of epilepsy, number of AEDs taken at time of randomization), and trial factors (concealed randomisation, blinding, losses to follow up) (Schulz 1995). Statistical heterogeneity was assessed using an I^2 summary statistic where 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. If heterogeneity was found, potential causes would have been explored (Kunz 1998). Provided no significant heterogeneity was found, results were synthesized using a fixed-effect model. Our preferred estimator is the relative risk ratio. For the outcomes 50% reduction in seizure frequency, and treatment withdrawal, 95% Confidence Intervals (CIs) are quoted.

Primary analysis included all patients in the treatment group to which they were allocated, irrespective of the treatment they actually received (intention-to-treat). For the efficacy outcome (50% or greater reduction in seizure frequency) three analyses were planned:

- Primary (intention to treat) analysis: patients not completing follow up or with inadequate seizure data were assumed non-responders.
- Worst case: patients not completing follow up or with inadequate seizure data were assumed non-responders in the oxcarbazepine group, and responders in the placebo group.
- Best case: patients not completing follow up or with inadequate seizure data were assumed responders in the oxcarbazepine group, and non-responders in the placebo group.

(2) Dose response analysis

We planned to examine the dose response relationships in the acquired aggregate data, using logistic regression, calculating probabilities for the following events for different doses:

(i) the percentage of patients having a 50% response (reduction in seizure frequency);
(ii) the difference in the percentage of patients responding to each dose compared to placebo.

A binary variable was defined with value 0 if the response was less than 50% and value 1 if the response was 50% or greater. Dose regression relationships were planned using logistic regression analysis, based on generalized linear models. Analysis was planned using the package GLIM, with that defined binary variable considered as the outcome variable (McCullagh 1989).

(3) Side effects

For individual listed side effects, 99% CIs are quoted making allowance for multiple testing.

(4) Cognitive and quality of life data

Data for these outcomes were summarized narratively.

RESULTS

Description of studies

We found four published parallel group studies meeting our inclusion criteria (Glauser 2000, Barcs 2000, Kraiprab 2005 and Pina-Garza 2005). Two of these studies were included in the previous version of this review (Glauser 1998 and Halasz 1998) for which we received unpublished data. Data for both trials were provided by Novartis, and both trials were undertaken as part of the pre-licensing evaluation of oxcarbazepine. Review authors were provided with copies of internal trial reports. We used data found in published reports for the other two studies.

Among them, these studies recruited 1128 patients, 267 by Glauser (Glauser 1998, Glauser 2000), 694 by Barcs (Halasz 1998, Barcs 2000), 39 by Kraiprab (Kraiprab 2005) and 128 by Pina-Garza (Pina-Garza 2005). Two studies were placebo controlled

and two were actively controlled. The actively controlled studies were included in this update.

One of the placebo controlled studies recruited only children (Glauser 2000), and had two treatment groups (oxcarbazepine and placebo). Dose was titrated according to weight: 20.0 - 29.0 kg, 900 mg/day; 29.1 - 39.0 kg, 1200 mg/day; 39.1 - 60.0 kg 1800 mg/day. The other placebo controlled study recruited adults (Barcs 2000), and had a placebo group and three oxcarbazepine groups (600 mg/day, 1200 mg/day, and 2400 mg/day). A significant proportion of patients in the 2400 mg group experienced problems with side effects requiring a reduction of dose. As a result the protocol was amended during the trial, and 43 of the 174 allocated to oxcarbazepine were titrated to 1800 mg/day.

Both placebo controlled studies had a similar design consisting of three phases. Firstly, both had a pre-randomization baseline phase of eight weeks duration. Secondly, both had a dose titration phase of two weeks duration. Thirdly, a maintenance period of 14 weeks in Glauser (Glauser 2000) and a maintenance period of 24 weeks duration in Barcs (Barcs 2000).

One of the actively controlled studies recruited only young children (Pina-Garza 2005), and compared doses 60mg/day and 10 mg/day. The other actively controlled study recruited adults (Kraiprab 2005) and compared (600mg/day and 1200 mg/day).

The Kraiprab (Kraiprab 2005) study design consisted of three phases. Firstly, a pre-randomization baseline phase of eight weeks duration. Secondly, a dose titration phase of two weeks duration. Thirdly, a maintenance period of 12 weeks duration. The Pina-Garza (Pina-Garza 2005) study design consisted of four phases. Firstly, had a pre-randomization screening phase phase of seven days duration. Secondly, an inpatient baseline period of 3 days duration. Thirdly, a dose titration phase of 26 days duration for the 60 mg/day group and zero days duration for the 10 mg/day group. Fourthly, a maintenance period of 9 days duration.

Three patients from Glauser (Glauser 2000) (one placebo, two oxcarbazepine) had been excluded from analyses, but have been reinstated for our intention-to-treat analysis, and contribute to our best and worst case analyses. These patients had been excluded because they failed to provide seizure data. Similarly, two patients were excluded from analyses in Halasz (Barcs 2000), (one oxcarbazepine 600 mg per day, one oxcarbazepine 1200 mg per day), but have been reinstated in our analyses. These two patients had been lost to follow up before starting trial medication.

Risk of bias in included studies

For two studies, allocation was concealed by providing sequentially numbered packages to each patient allocated to treatment. Allocation sequence generation was In Barcs (Barcs 2000), the random list was generated using random permuted blocks of four. In Glauser (Glauser 2000) the random list was computer generated, which was confirmed to the review authors by Novartis Pharma. For Pina Garza (Pina Garza 2005) sequence generation was made via an automated voice response system, no details were given however on how allocation was concealed.

In all four studies, medication was supplied by the drug sponsor. Blinding was maintained by using identical packaging and medications for three studies (Glauser 2000, Barcs 2000 and Kraiprab 2005). In Pina-Garza (Pina-Garza 2005) patients were not blinded but raters were blinded to the medication allocated. Randomization codes were not broken until all data had been collected. Intention to treat data have been provided for all four of the trials. Incomplte outcomes were addresses in three trials adequately (Glauser 2000, Barcs 2000 and Pina-Garza 2005). There were no incomplete outcomes in Kariparb.

Our analysis of the risk of bias we deemed that Glauser was free form bias, Barcs 2000 gave no details of sequence generation. Allocation concealment was deemed inadequate in Pina Garza.

Effects of interventions

Seperate analyses were undertaken for the placebo controlled and the actively controlled trials. Each analysis included one trial recruiting children and one trial recruiting adults.

50% or greater reduction in seizure frequency

For any dose of oxcarbazepine versus placebo from Glauser (Glauser 2000) and Barcs (Barcs 2000), I^2 = 71% which indicates that there may be some substantial heterogeneity present. This might be explained by the fact that there are only two studies, one of which is in children and the other in adults, and which used different dosing strategies. The overall risk ratio (95% CI) was 2.51 (1.89, 3.34). The estimate for the paediatric study (Glauser 2000) was 1.84 (1.25, 2.70), which was lower that the estimate for the adult study (Barcs 2000), 3.11 (2.07, 4.66). The data here are insufficient to comment upon the effect of age on response to oxcarbazepine. The confidence intervals clearly overlap, and the difference in estimates could be explained by random error.

Barcs (Barcs 2000) was the only study for which the effect of dose could be investigated using aggregate data. As a result we were unable to undertake planned dose regression analyses. We have therefore estimated risk ratios for each dose compared to placebo for this study with the following results: 600 mg per day 2.11 (1.32, 3.35); 1200 mg per day 3.24 (2.11, 4.98); 2400 mg per day 3.93 (2.59, 5.97). These results indicate increasing efficacy with increasing dose, with no clear plateau at doses tested.

Three patients in the Glauser study (Glauser 2000) and two patients from Barcs (Barcs 2000) were excluded from the reported analyses as no seizure data were recorded. All 3 patients in Glauser (Glauser 2000) received trial treatment before withdrawal are reinstated for our intention-to-treat analyses. The two patients in Barcs (Barcs 2000) did not receive any trial treatment before withdrawal so are not reinstated for our intention-to-treat analyses.

For high dose (1200 mg/day) versus low dose (600 mg/day) in Kraiprab (Kraiprab 2005), the risk ratio (95% CI) for this adult study was 1.17 (0.61, 2.23).

For high dose (60 mg/day) versus low dose (10 mg/day) in Pina-Garza (Pina-Garza 2005) the risk ratio (95% CI) for this paediatric study was 1.37 (0.99, 1.88).

Treatment withdrawal

For any dose of oxcarbazepine versus placebo from Glauser (Glauser 2000) and Barcs (Barcs 2000), I^2 = 0% which indicates heterogeneity might not be important. The overall risk ratio (95% CIs) for withdrawal for any reason was 1.72 (1.36, 2.19), indicating that patients are significantly more likely to withdraw from oxcarbazepine than placebo. Estimates for individual doses from Barcs (Barcs 2000) indicates that patients were increasingly more likely to withdraw from oxcarbazepine with increasing dose: 600 mg 0.82 (0.57, 1.18); 1200 mg 1.62 (1.21, 2.15), 2400 mg 2.60 (2.02, 3.35).

For high dose of oxcarbazepine (1200 mg/day) versus low dose of oxcarbazepine (600 mg/day) in Kraiprab (Kraiprab 2005), the risk ratio (95% CI) for this adult study was 0.53 (0.05, 5.34).

For high dose of oxcarbazepine (60 mg/day) versus low dose of oxcarbazepine (10 mg/day) in Pina-Garza (Pina-Garza 2005) the risk ratio (95% CI) for this paediatric study was 1.60 (0.55, 4.63).

Side effects

For any dose of oxcarbazepine versus placebo from Glauser (Glauser 2000) and Barcs (Barcs 2000), the following side effects were significantly associated with oxcarbazepine (risk ratio 99%CI): any adverse event 1.16 (1.06, 1.26); ataxia 3.54 (1.75, 7.13); dizziness 2.87 (1.82, 4.52); nausea 3.09 (1.74, 5.49); somnolence 2.36 (1.54, 3.62); diplopia 7.25 (3.12, 16.80); abnormal gait 5.54 (1.74, 17.64); nystagmus 4.58 (1.91, 10.97). Data on the number of patients with hyponatraemia were not reported in Glauser (Glauser 2000).

For any high dose of oxcarbazepine (1200 mg/day) versus low dose of oxcarbazepine (600 mg/day) from Kraiprab (Kraiprab 2005), there were no side effects that were significantly associated with the higher dose of oxcarbazepine. Data on the number of patients with hyponatremia were not reported.

For any high dose of oxcarbazepine (60 mg/day) versus low dose of oxcarbazepine (10 mg/day) from Pina-Garza (Pina-Garza 2005), the following side effects were significantly associated with the higher dose of oxcarbazepine (risk ratio 95%CI): any adverse event 1.18 (1.30, 2.52); infections and infestations 2.78 (1.41, 5.48); somnolence3.78 (1.11, 12.92). Data on the number of patients with hyponatremia were not reported.

Cognitive and quality of life data

These outcomes were not assessed in included trials.

DISCUSSION

We included four trials of oxcarbazepine in patients with refractory focal epilepsy. Two trials compared oxcarbazepine with placebo and two trials compared two dosages of oxcarbazepine. Results of the placebo controlled trials have been summarised in a meta-analysis, but could not be undertaken for the actively controlled trials.

Glauser 2000 and Barcs 2000 used adequate methods of concealment of randomization and were double-blinded. In addition, we were able to acquire data for intention-to-treat analyses. Both trials included in this review were sponsored by Novartis as part of their pre-licensing evaluation of oxcarbazepine. One trial recruited children and the other adults. It seemed reasonable to the authors to combine these two studies in a meta-analysis given that all those recruited had drug-resistant partial epilepsy, and that the methods used in the trials were similar. Pina-Garza 2005 and Kraiprab 2005 compared high and low dose oxcarbazepine and it would not be reasonable to meta-analyse these two due to disparity in the comparator dose.

The results from the analysis of placebo controlled trials show that oxcarbazepine reduces seizure frequency when used as an add-on antiepileptic drug (AED) in patients with drug-resistant partial epilepsy. Due to insufficient data, we were unable to undertake the planned dose response regression analyses. However, analysis of data from the adult study (Barcs 2000) shows increasing efficacy with increasing dose, with no clear indication of plateauing of effect at doses tested. Interestingly, the overall estimate of efficacy was greater in the adult study than the paediatric study. Given the fact that this result may represent random error, and differences in dosing, no conclusions can be drawn about the relative effect of oxcarbazepine on adults and children. Results for the outcome 'withdrawal of allocated treatment' show that oxcarbazepine is significantly more likely to be withdrawn than placebo for doses higher than 600 mg per day. In trials of relatively short duration, such as the two reviewed here, this is likely to represent problems with tolerability rather than poor seizure control.With respect to side effects, ataxia, dizziness, fatigue, nausea, somnolence, and diplopia were significantly more likely to occur in the oxcarbazepine treated group. These findings are in keeping with the significant treatment withdrawal associated with oxcarbazepine. Current data available are insufficient to delineate a precise adverse effects profile for oxcarbazepine.

Due to differences in design we were unable to undertake a meta-analysis of the two trials that compared high and low doses of oxcarbazepine. The individual trials found no difference between doses for efficacy when comparing high and low dose oxcarbazepine,. Kraiprab (Kraiprab 2005) found no difference in treatment withdrawal or adverse effects, while adverse effects were poorly reported in PinaGarza preventing a comprehensive analysis. Overall there were more adverse events in the high dose group.

Although the results of this review indicate that oxcarbazepine is an effective add-on AED for patients with drug-resistant partial epilepsy in the short-term (four to six months), it does not tell us how effective it is in the long-term. This is important given that epilepsy is a chronic condition. This review does not inform us how

oxcarbazepine compares with other AEDs in the same scenario. This is an extremely important issue for clinicians and those with epilepsy who are faced with an ever increasing number of AEDs to choose from. Reliable evidence informing that decision will need to come from randomised head to head trials.

In addition, the results of this review do not inform us of the effects of oxcarbazepine when used as monotherapy. Monotherapy trials comparing oxcarbazepine with carbamazepine, phenytoin and valproate have been undertaken, and will contribute to future individual patient data reviews to be undertaken by members of the Cochrane Epilepsy Group. Also, the results of this review cannot be extrapolated to those with a generalized epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

In people with drug-resistant partial epilepsy, oxcarbazepine has efficacy as an add-on treatment both in an adult population and a paediatric one. In adults efficacy has been demonstrated for doses between 600 mg and 2400 mg per day, however, the 2400 mg per day dose was poorly tolerated. As stated in 'Characteristics of the included studies', the paediatric trial was conducted defining the optimum daily dose as the lowest one which provided maximum seizure control with acceptable tolerability; therefore, oxcarbazepine has shown efficacy as add-on treatment in this population between doses of 900 mg/day (20.0 to 29.0 kg) to 1800 mg/day (39.1 to 60.0 kg). Two studies examined dose relationship in adults and children, there was no difference in efficacy or safety outcomes when a higher dose was used.

Two other studies compared high versus low dose of oxcarbazepine. The study in adults was poorly powered and failed to find any difference between high versus low dose regimens.

Implications for research

Further trials of oxcarbazepine are required to assess the following:

(1) the long-term efficacy and safety of add-on oxcarbazepine;

(2) how oxcarbazepine compares with other add-on treatments in drug-resistant partial epilepsy;

(3) the doses response relationship of add-on oxcarbazepine in adults and children; using a larger cohort of patients to increase the power of the study

(4) the role of oxcarbazepine in generalized epilepsy;

(5) how oxcarbazepine compares with standard AEDs such as monotherapy;

(6) effects of oxcarbazepine on quality of life and cognition;

(7) economic aspects of oxcarbazepine therapy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barcs 2000

Methods	Randomized double blind placebo controlled parallel group trial 4 treatment groups, placebo, 600, 1200 and 2400 mg/day oxcarbazepine Randomization concealed by allocating sequentially packed containers Double blinded using identical preparations and packaging. Pre-randomization baseline period of 8 weeks. Treatment period of 26 weeks. Treatment period consisted of a 2 week titration period and a 24 week maintenance period
Participants	Multi-national, multi-centre study recruiting 694 adults aged 15 - 65 years Taking no more than 3 standard antiepileptic drugs. All had drug-resistant seizures. Patients could have either simple or complex uncontrolled partial seizures with or without secondary generalisation
Interventions	169 allocated to 600 mg/day oxcarbazepine, 178 to 1200 mg/day oxcarbazepine, 174 to 2400 mg/day oxcarbazepine and 173 to placebo
Outcomes	Percentage change in seizure frequency (simple or complex partial onset seizure with or without generalisation) 50% or greater reduction in seizure frequency. Total number of seizures. Side effects. Liverpool seizure severity scale.
Notes	The 2400 mg/day was poorly tolerated, and the trial protocol was amended, with 43 out of 174 patients titrated to 1800 mg/day instead 2 patients (1 taking 600 mg/day oxcarbazepine and the other 1200 mg/day placebo) had been excluded from reported analyses as no seizure data were recorded. Both patients received no trial treatment they will not contribute to the review primary (intention to treat) analysis. These patients contribute to the best and worst case sensitivity analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random list generated by permutated blocks of four
Allocation concealment (selection bias)	Low risk	Adequate.conclealed in packed containers
Blinding (performance bias and detection bias) All outcomes	Low risk	Double Blinded Study.

Barcs 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double Blinded Study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double Blinded Study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients were excluded, one form the 1200mg group and one from the 600mg group
Selective reporting (reporting bias)	Low risk	See ORBIT tool, this paper was deemed low risk of bias of selective outcome reporting

Glauser 2000

Methods	Randomized double blind placebo controlled parallel group trial Randomization concealed by allocating sequentially packed containers. Allocation was made using a computer generated schedule Double blinded using identical preparations and packaging. Pre-randomization baseline period of 8 weeks. Treatment period of 16 weeks (including 2 week titration period)
Participants	Multi-national, multi-centre study recruiting 267 children aged between 3 and 17 years All had drug-resistant partial seizures. Patients in either groups took the following background drugs: Carbamzepine, valproate and lamotrigine and phenytoin. There was no difference in proportions between these groups. Patients were either on one or two concomitant AEDs Median baseline partial seizure frequency per 28 days in the placebo group was 13 (range 2 to 554) and 12 in the oxcarbazepine group (range 3 to 1470)
Interventions	138 allocated oxcarbazepine, 129 placebo. Dose of oxcarbazepine was allocated according to weight: 20.0 - 29.0 kg 900 mg/day 29.1 - 39.0 kg 1200 mg/day 39.1 - 60.0 kg 1800 mg/day
Outcomes	Percentage change in seizure frequency. 50% or greater reduction in seizure frequency. Percentage change in secondary generalised seizure frequency from baseline Percentage change in simple partial seizure frequency from baseline Percentage change in complex partial seizure frequency from baseline Adverse events.

Notes	3 patients (2 oxcarbazepine, 1 placebo) had been excluded from reported analyses as no data were recorded. All 3 patients received trial treatment so will contribute to the review primary (intention to treat) analysis as non-responders. These patients contribute to the best and worst case sensitivity analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation made via computer generated schedule.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double Blinded Study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double Blinded Study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double Blinded Study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for two patients excluded were provided.
Selective reporting (reporting bias)	Low risk	See ORBIT tool, this paper was deemed low risk of bias of selective outcome reporting

Kraiprab 2005

Methods	Randomised double blind parallel group trial. Two treatment groups, oxcarbazepine 600mg and 1200mg. Double blinded using identical packaging and both concealed using identical capsules Details of allocation were not reported. Baseline Period of 8 weeks. Treatment Period of 14 weeks (2 week titration and 12 week maintenance)
Participants	Single-centre study recruiting thirty nine adults 18-65 years of age Patients were taking one or more standard antiepileptic drugs having previously failed treatment on any available AEDs Patients with partial seizures. Patients in each group were taking 1 to 3 AEDs but no details given in the names of these. Sixty eight percent of the higher dose group (1200mg/day) were on monotherapy

Kraiprab 2005 (*Continued*)

	compared with 35% of the low dose group (600mg/day) taking monotherapy
Interventions	Twenty patients were allocated to 600mg per day of oxcarbazepine Nineteen patients were allocated to 1200mg per day of oxcarbazepine Comparator in the low dose group.
Outcomes	Percentage reduction in seizure frequency per 28 days during the double blind treatment phase relative to the baseline Fifty percent or more reduction in seizure frequency per 28 days Incidence of adverse events.
Notes	One patient in the 1200mg group was lost to follow up and three patients discontinued due to adverse events. Both patients received trial treatment so will contribute to the review primary (intention to treat) analysis as non-responders. These patients contribute to the best and worst case sensitivity analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No mention of sequence generation given.
Allocation concealment (selection bias)	High risk	Details of allocation not given.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded using identical packaging.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double Blinded Study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double Blinded Study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported.
Selective reporting (reporting bias)	High risk	Authors also quoted the reduction in seizure frequency in the patients taking carbamazepine as a separate outcome but they did not state they would do this in the methods section

Pina-Garza 2005

Methods	Randomised rater blinded parallel group study. Two treatment groups where one is the active comparator: oxcarbazepine 10mg/day versus oxcarbazepine 10-60mg/day
Participants	Children aged one month to less than four years of age. Patients with partial seizures. Patients with one to two concomitant AEDs. Patients admitted for EEG monitoring to detect seizure activity Sixty four patients randomised into the high dose groups but only 59 analysed and 64 randomised to the low dose group with only 57 analysed
Interventions	Sixty four patients were allocated to the low dose group (10mg/day) for a period of nine days maintenance Sixty four patients were allocated to the high dose group (10-60mg/day) for a period of 26 titration and nine days maintenance
Outcomes	Absolute change in seizure frequency per 24 hours during the treatment phase compared to baseline Percentage change in seizure frequency per 24 hours during the treatment phase compared to baseline Fifty percent or more reduction in seizure frequency per 24 hours
Notes	Two patients in each group were dropped out as consent was withdrawn. Two patients in the low dose group withdrew due to adverse events compared to three in the high dose group. One patient in the low dose group withdrew due to lack of efficacy and three in the high dose group withdrew due to lack of efficacy. All 13 patients received trial treatment so will contribute to the review primary (intention to treat) analysis as non-responders. These patients contribute to the best and worst case sensitivity analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Automated voice response system that allocated treatment randomly
Allocation concealment (selection bias)	Unclear risk	No details of allocation provided in the published reports.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients were not blinded for ethical reasons. Pharmacy was not blinded but raters were blinded to treatment. Thus this trial was single blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were not blinded for ethical reasons. Pharmacy was not blinded but raters were blinded to treatment. Thus this trial was single blinded

Pina-Garza 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Rater Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy outcomes were fully reported hence there was no incomplete reporting. Tolerability outcomes were fully reported too. Adverse events were reported but authors did not use a validated dictionary making it difficult to be used in this review
Selective reporting (reporting bias)	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Houtkooper 1987	This is a randomised, double-blind, cross-over study, replacing oxcarbazepine for carbamazepine in 48 in-patients with epilepsy. Therefore, it was not an add-on placebo controlled trial

DATA AND ANALYSES

Comparison 1. Efficacy of oxcarbazepine in add-on versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of responders : The proportion of patients with a 50 % or greater reduction in seizure frequency	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oxcarbazepine 600 mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.32, 3.35]
1.2 Oxcarbazepine 1200 mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [2.11, 4.98]
1.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [2.59, 5.97]
1.4 Oxcarbazepine any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.89, 3.34]

Comparison 2. Global effectiveness of oxcarbazepine in add-on versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of patients having treatment withdrawn during the course of the treatment period	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oxcarbazepine 600 mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.18]
1.2 Oxcarbazepine 1200 mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.21, 2.15]
1.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [2.02, 3.35]
1.4 Oxcarbazepine any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.36, 2.19]

Comparison 3. Side effects of oxcarbazepine in add-on versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abdominal Pain	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oxcarbazepine 600mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.91, 4.68]
1.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.23, 5.87]
1.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.75, 4.04]
1.4 Oxcarbazepine Anydose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.89, 2.47]
2 Abnormal Gait	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Oxcarbazepine 600mg/dayversus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	4.63 [1.02, 21.13]
2.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	8.31 [1.95, 35.42]
2.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	12.93 [3.12, 53.62]
2.4 Oxcarbazepine Any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	5.54 [2.29, 13.38]
3 Ataxia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.83, 4.00]
3.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [1.64, 6.82]
3.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	6.19 [3.16, 12.11]
3.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	3.54 [2.07, 6.03]
4 Diplopia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [1.35, 6.39]
4.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	6.56 [3.22, 13.38]
4.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	8.45 [4.19, 17.05]
4.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	7.25 [3.82, 13.74]
5 Dizziness	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.22, 3.13]
5.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.58, 3.87]

5.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [2.18, 5.13]
5.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [2.03, 4.05]
6 Fatigue	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.11, 4.11]
6.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.86, 3.35]
6.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.12, 4.13]
6.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.15, 2.85]
7 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Oxcarbazepine any dose versus placebo	1	267	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.56, 1.72]
8 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.95, 1.91]
8.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.79, 1.63]
8.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.66, 1.42]
8.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.04, 1.70]
9 Hyponatremia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Oxcarbazepine 600 mg/day versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Oxcarbazepine 1200 mg/day versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Oxcarbazepine any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.35]
10 Nausea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.98, 3.39]
10.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [1.70, 5.26]
10.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	3.48 [2.00, 6.06]

10.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [2.00, 4.78]
11 Nystagmus	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Oxcarbazepine 600mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.64, 4.07]
11.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [2.30, 10.99]
11.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	5.82 [2.69, 12.62]
11.4 Oxcarbazepine Any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [2.35, 8.90]
12 Vertigo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.91, 8.67]
12.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	4.86 [1.70, 13.93]
12.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	5.97 [2.11, 16.83]
12.4 Oxcarbazepine any dose versus placebo	1	694	Risk Ratio (M-H, Fixed, 95% CI)	4.57 [1.68, 12.41]
13 Rash	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Oxcarbazepine 600 mg/day versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Oxcarbazepine 1200 mg/day versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.4 Oxcarbazepine any dose versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Somnolence	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Oxcarbazepine 600 mg/day versus placebo	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.01, 2.82]
14.2 Oxcarbazepine 1200 mg/day versus placebo	1	351	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.45, 3.76]
14.3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.75, 4.43]
14.4 Oxcarbazepine any dose versus placebo	2	961	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.70, 3.27]
15 Tremor	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Oxcarbazepine 600mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.30, 2.57]
15.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.81, 4.73]
15.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [1.58, 7.99]

15.4 Oxcarbazepine any dose versus placebo	1	692	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.98, 4.66]
16 Viral Infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Oxcarbazepine 600mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.49]
16.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.39, 1.24]
16.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.20, 0.84]
16.4 Oxcarbazepine Any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.51, 1.04]
17 Any Adverse Event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Oxcarbazepine 600mg/day versus placebo	1	341	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.22]
17.2 Oxcarbazepine 1200mg/day versus placebo	1	350	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.08, 1.30]
17.3 Oxcarbazepine 2400mg/day versus placebo	1	347	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.17, 1.40]
17.4 Oxcarbazepine any dose versus placebo	2	959	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.08, 1.24]

Comparison 4. Efficacy of oxcarbazepine in add-on; high dose versus low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of responders: The proportion of patients with a 50% or greater reduction in seizure frequency	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 5. Global effectiveness of oxcarbazepine in add-on; high dose versus low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients having treatment withdrawn during the course of treatment period	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 6. Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proprtion of patients having any adverse event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Infections	1	128	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.41, 5.48]
3 Somnolence	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Ataxia	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.29, 1.96]
5 Dizziness	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.87, 9.03]
6 Headache	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.24, 4.59]
7 Abnornal vision	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.20, 3.07]
8 Diplopia	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 15.66]
9 Vomiting	1	39	Risk Ratio (M-H, Fixed, 95% CI)	5.25 [0.27, 102.74]
10 Nausea	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 15.66]
11 Fatigue	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.05, 5.34]
12 Rash	1	39	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.14, 72.88]

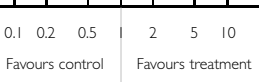
Analysis 1.1. Comparison 1 Efficacy of oxcarbazepine in add-on versus placebo, Outcome 1 Proportion of responders : The proportion of patients with a 50 % or greater reduction in seizure frequency.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 1 Efficacy of oxcarbazepine in add-on versus placebo

Outcome: 1 Proportion of responders : The proportion of patients with a 50 % or greater reduction in seizure frequency

Study or subgroup	Treatment : OXC n/N	Control : Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oxcarbazepine 600 mg/day versus placebo					
Barcs 2000	45/168	22/173		100.0 %	2.11 [1.32, 3.35]
Subtotal (95% CI)	**168**	**173**		**100.0 %**	**2.11 [1.32, 3.35]**
Total events: 45 (Treatment : OXC), 22 (Control : Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.15 (P = 0.0016)					
2 Oxcarbazepine 1200 mg/day versus placebo					
Barcs 2000	73/177	22/173		100.0 %	3.24 [2.11, 4.98]
Subtotal (95% CI)	**177**	**173**		**100.0 %**	**3.24 [2.11, 4.98]**
Total events: 73 (Treatment : OXC), 22 (Control : Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.39 (P < 0.00001)					
3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo					



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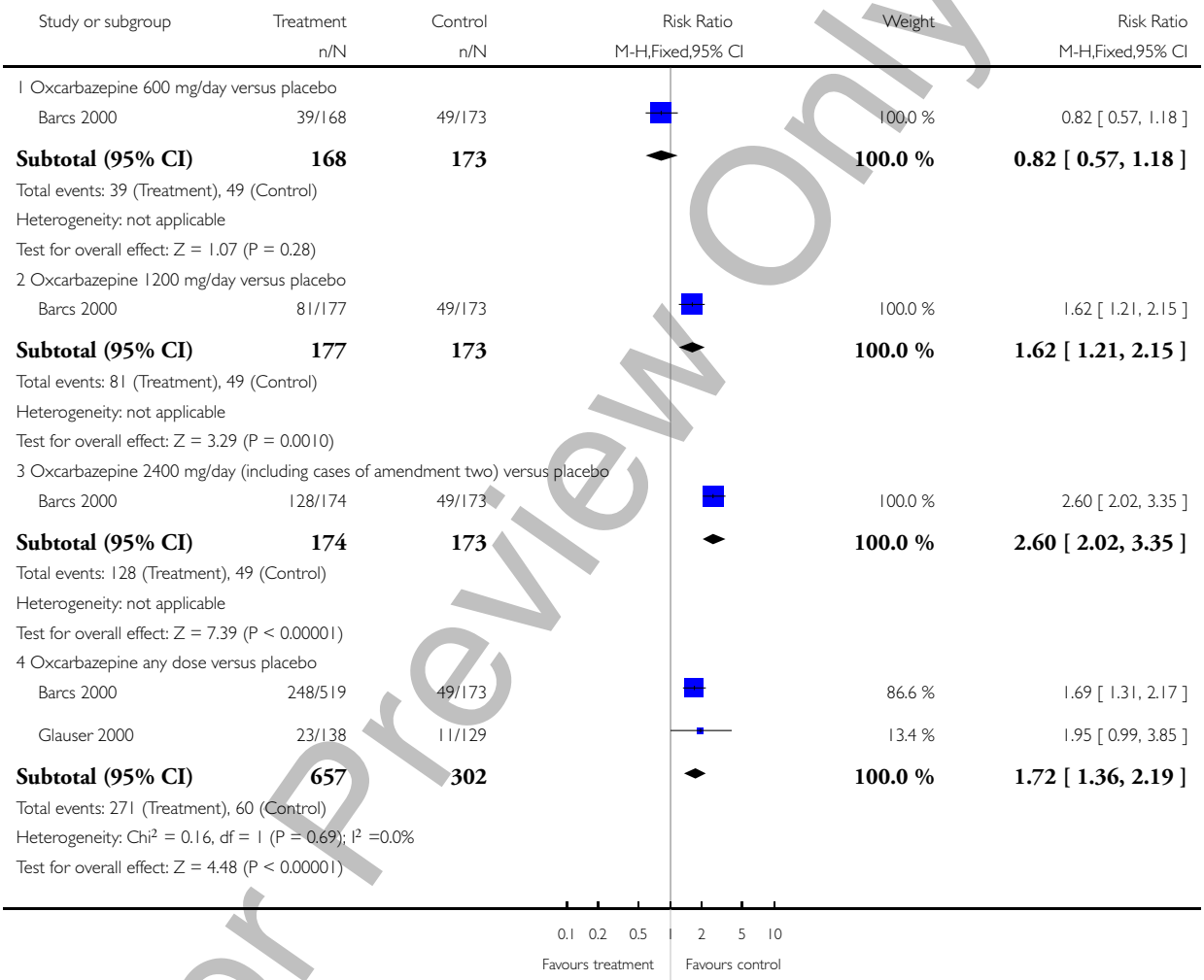
Study or subgroup	Treatment : OXC n/N	Control : Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Barcs 2000	87/174	22/173		100.0 %	3.93 [2.59, 5.97]
Subtotal (95% CI)	**174**	**173**		**100.0 %**	**3.93 [2.59, 5.97]**
Total events: 87 (Treatment : OXC), 22 (Control : Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.42 (P < 0.00001)					
4 Oxcarbazepine any dose versus placebo					
Barcs 2000	205/519	22/173		53.3 %	3.11 [2.07, 4.66]
Glauser 2000	55/138	28/129		46.7 %	1.84 [1.25, 2.70]
Subtotal (95% CI)	**657**	**302**		**100.0 %**	**2.51 [1.89, 3.34]**
Total events: 260 (Treatment : OXC), 50 (Control : Placebo)					
Heterogeneity: Chi^2 = 3.58, df = 1 (P = 0.06); I^2 =72%					
Test for overall effect: Z = 6.33 (P < 0.00001)					

Analysis 2.1. Comparison 2 Global effectiveness of oxcarbazepine in add-on versus placebo, Outcome 1 The proportion of patients having treatment withdrawn during the course of the treatment period.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 2 Global effectiveness of oxcarbazepine in add-on versus placebo

Outcome: 1 The proportion of patients having treatment withdrawn during the course of the treatment period



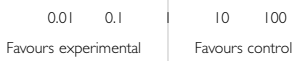
Analysis 3.1. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 1 Abdominal Pain.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 1 Abdominal Pain

Study or subgroup	Oxcarbazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oxcarbazepine 600mg/day versus placebo					
Barcs 2000	16/168	8/173		100.0 %	2.06 [0.91, 4.68]
Subtotal (95% CI)	**168**	**173**		**100.0 %**	**2.06 [0.91, 4.68]**
Total events: 16 (Oxcarbazepine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.72 (P = 0.085)					
2 Oxcarbazepine 1200mg/day versus placebo					
Barcs 2000	22/177	8/173		100.0 %	2.69 [1.23, 5.87]
Subtotal (95% CI)	**177**	**173**		**100.0 %**	**2.69 [1.23, 5.87]**
Total events: 22 (Oxcarbazepine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.48 (P = 0.013)					
3 Oxcarbazepine 2400mg/day versus placebo					
Barcs 2000	14/174	8/173		100.0 %	1.74 [0.75, 4.04]
Subtotal (95% CI)	**174**	**173**		**100.0 %**	**1.74 [0.75, 4.04]**
Total events: 14 (Oxcarbazepine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
4 Oxcarbazepine Anydose versus placebo					
Glauser 2000	12/138	13/129		52.8 %	0.86 [0.41, 1.82]
Barcs 2000	52/519	8/173		47.2 %	2.17 [1.05, 4.47]
Subtotal (95% CI)	**657**	**302**		**100.0 %**	**1.48 [0.89, 2.47]**
Total events: 64 (Oxcarbazepine), 21 (Placebo)					
Heterogeneity: Chi^2 = 3.07, df = 1 (P = 0.08); I^2 =67%					
Test for overall effect: Z = 1.50 (P = 0.13)					

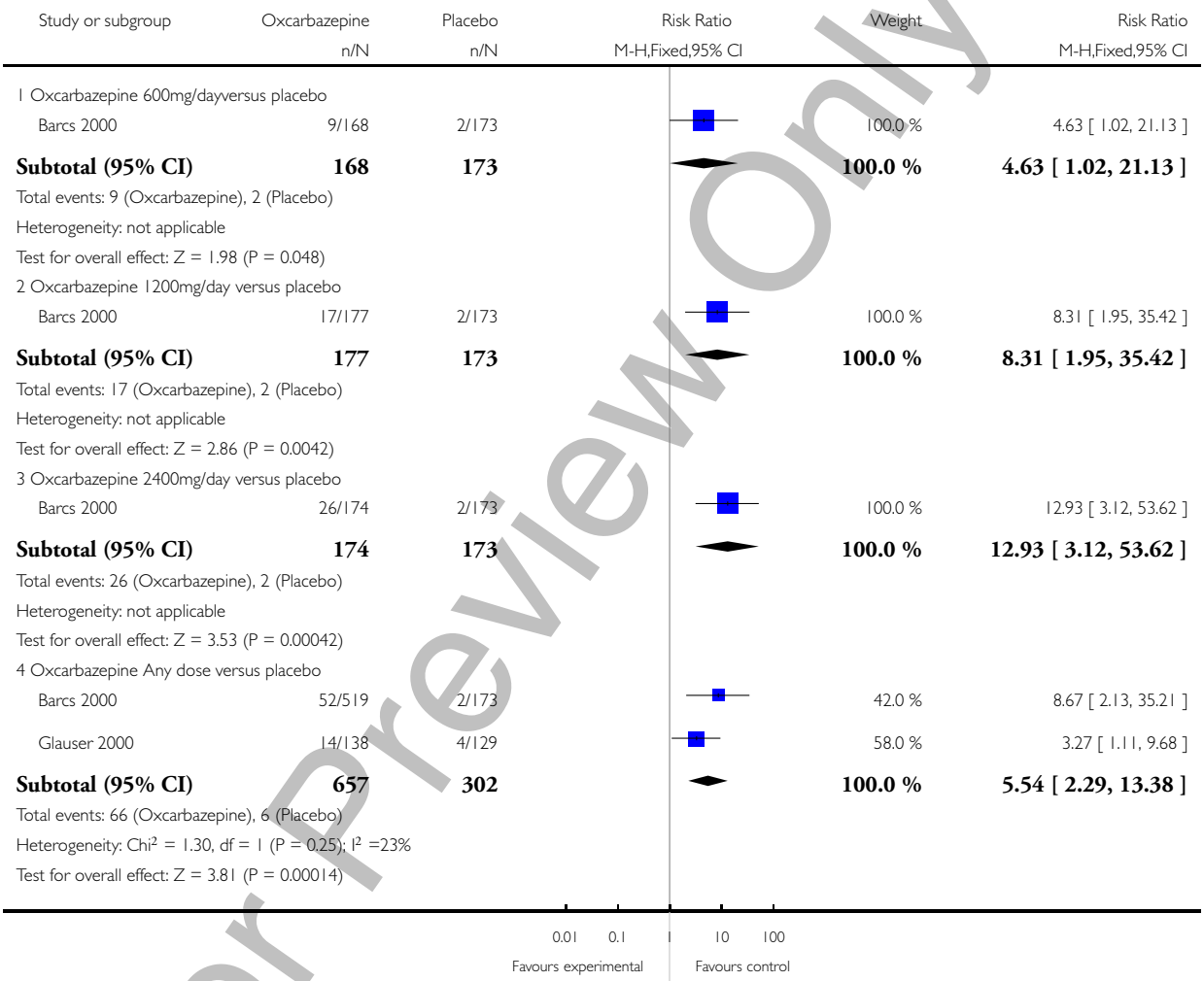


Analysis 3.2. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 2 Abnormal Gait.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 2 Abnormal Gait

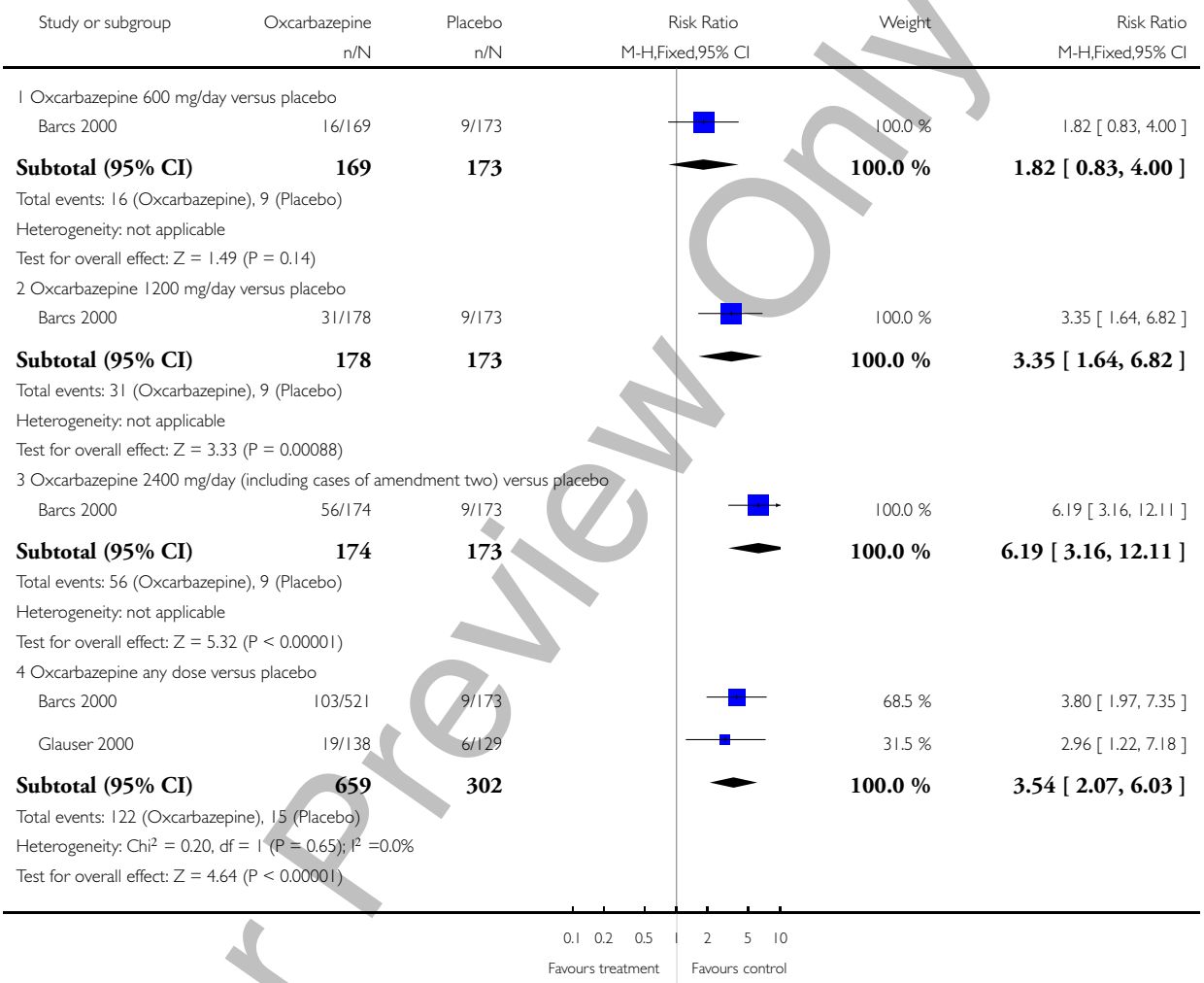


Analysis 3.3. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 3 Ataxia.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 3 Ataxia

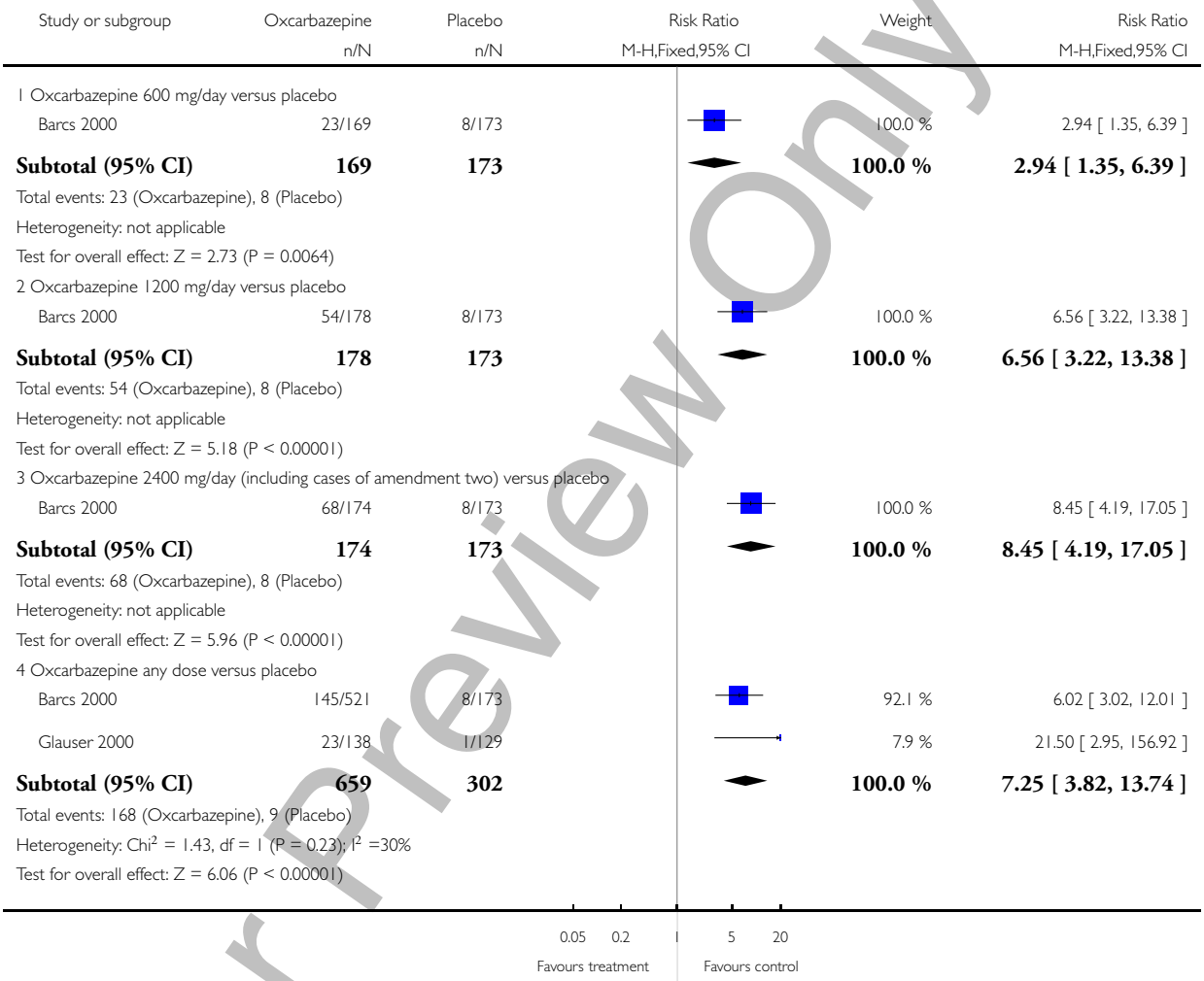


Analysis 3.4. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 4 Diplopia.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 4 Diplopia

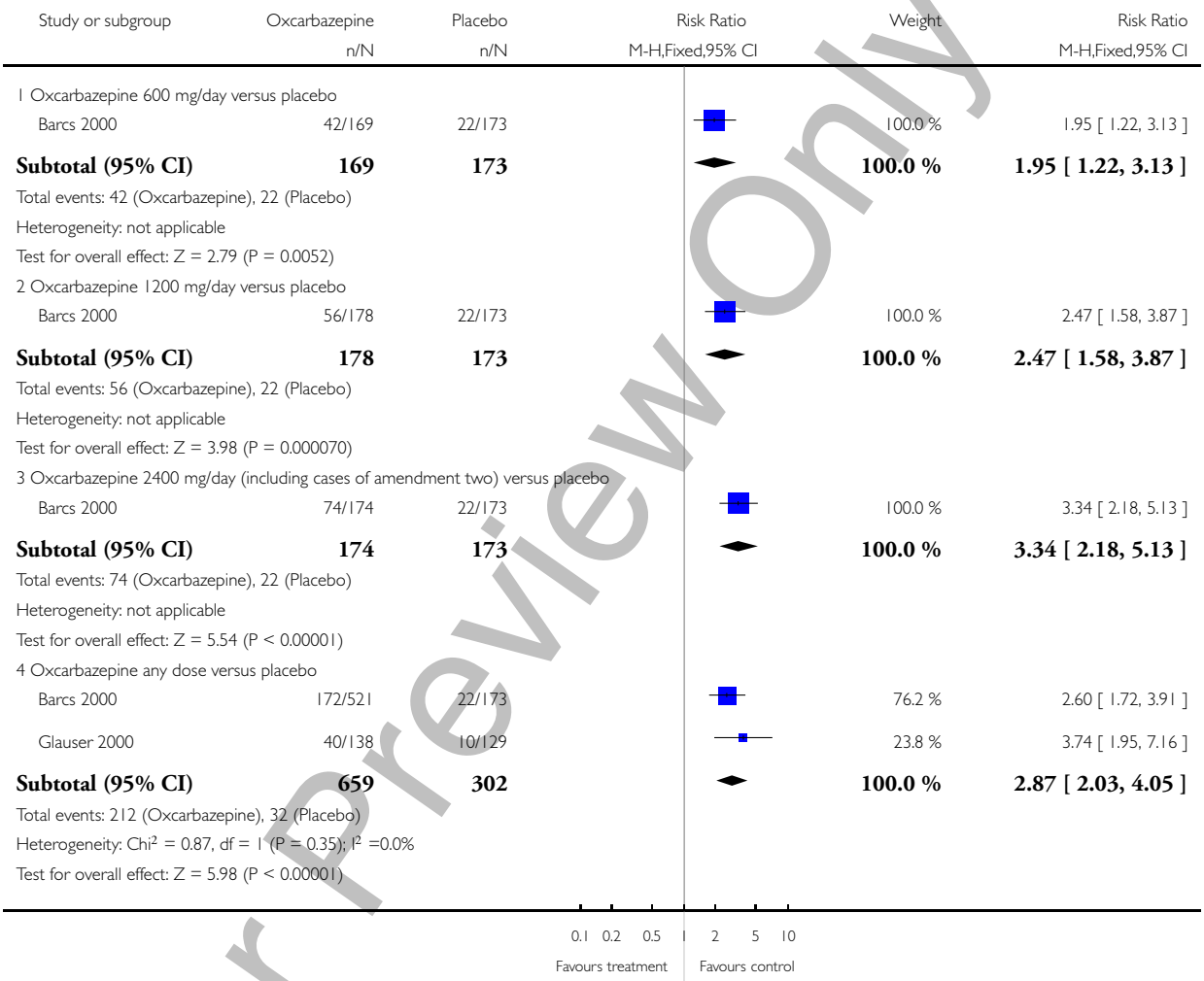


Analysis 3.5. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 5 Dizziness.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 5 Dizziness

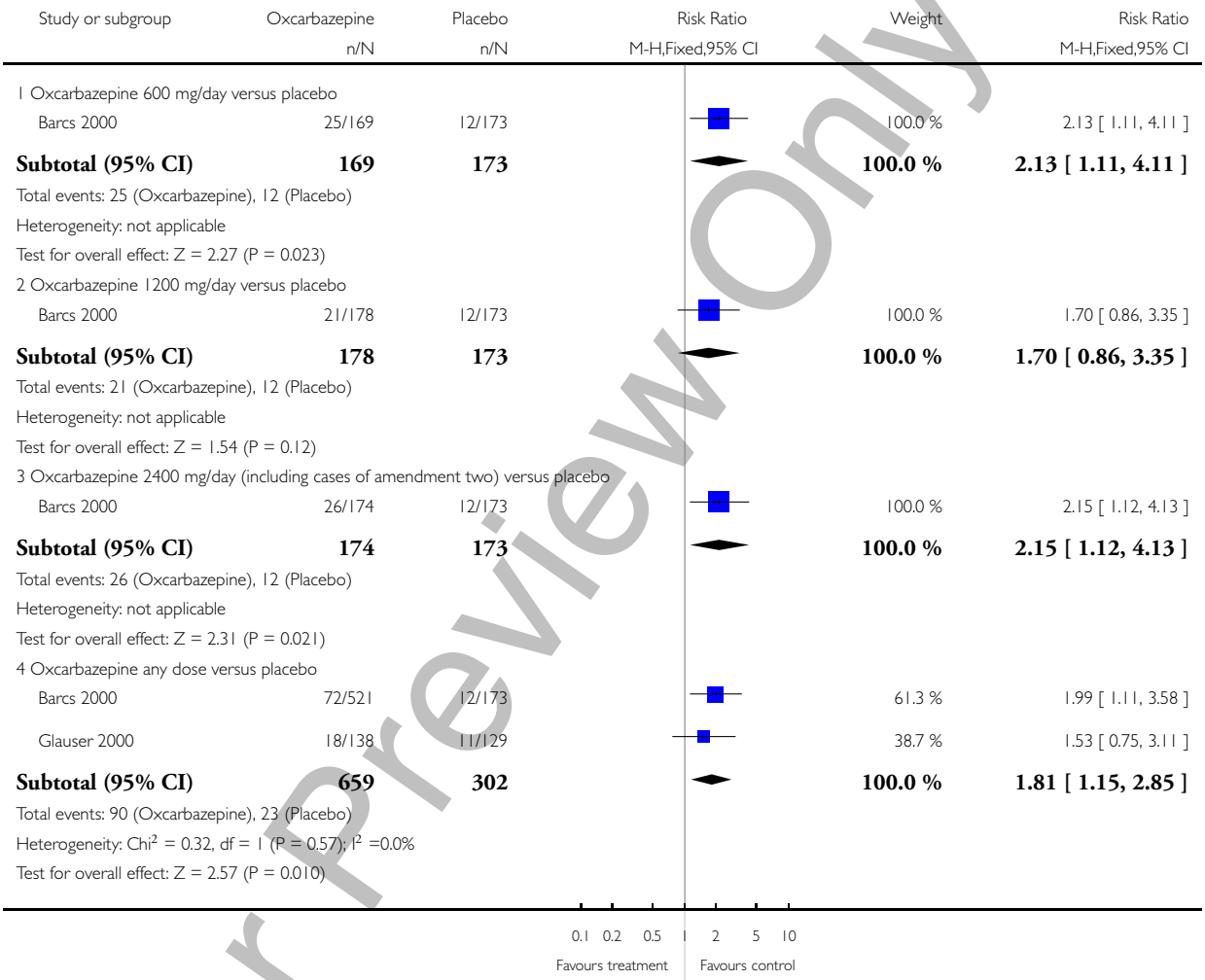


Analysis 3.6. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 6 Fatigue.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 6 Fatigue

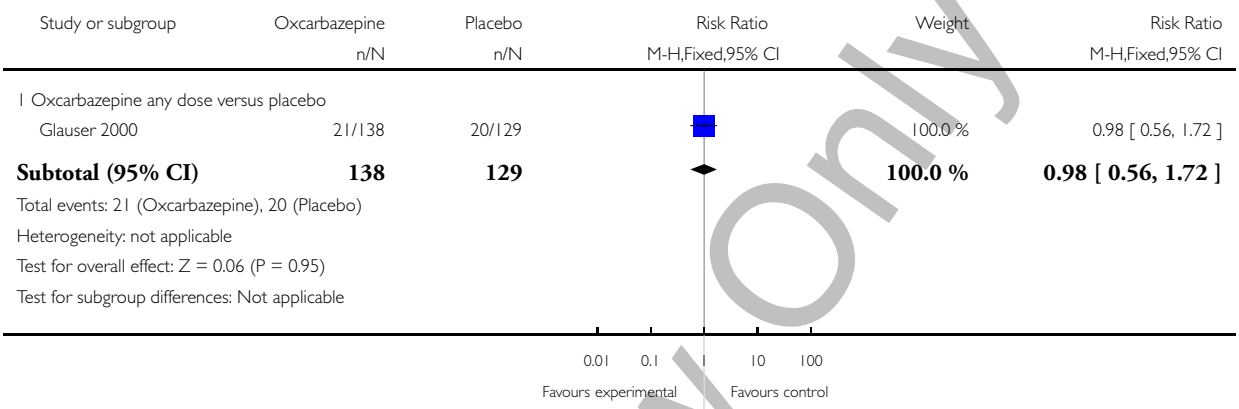


Analysis 3.7. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 7 Fever.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 7 Fever

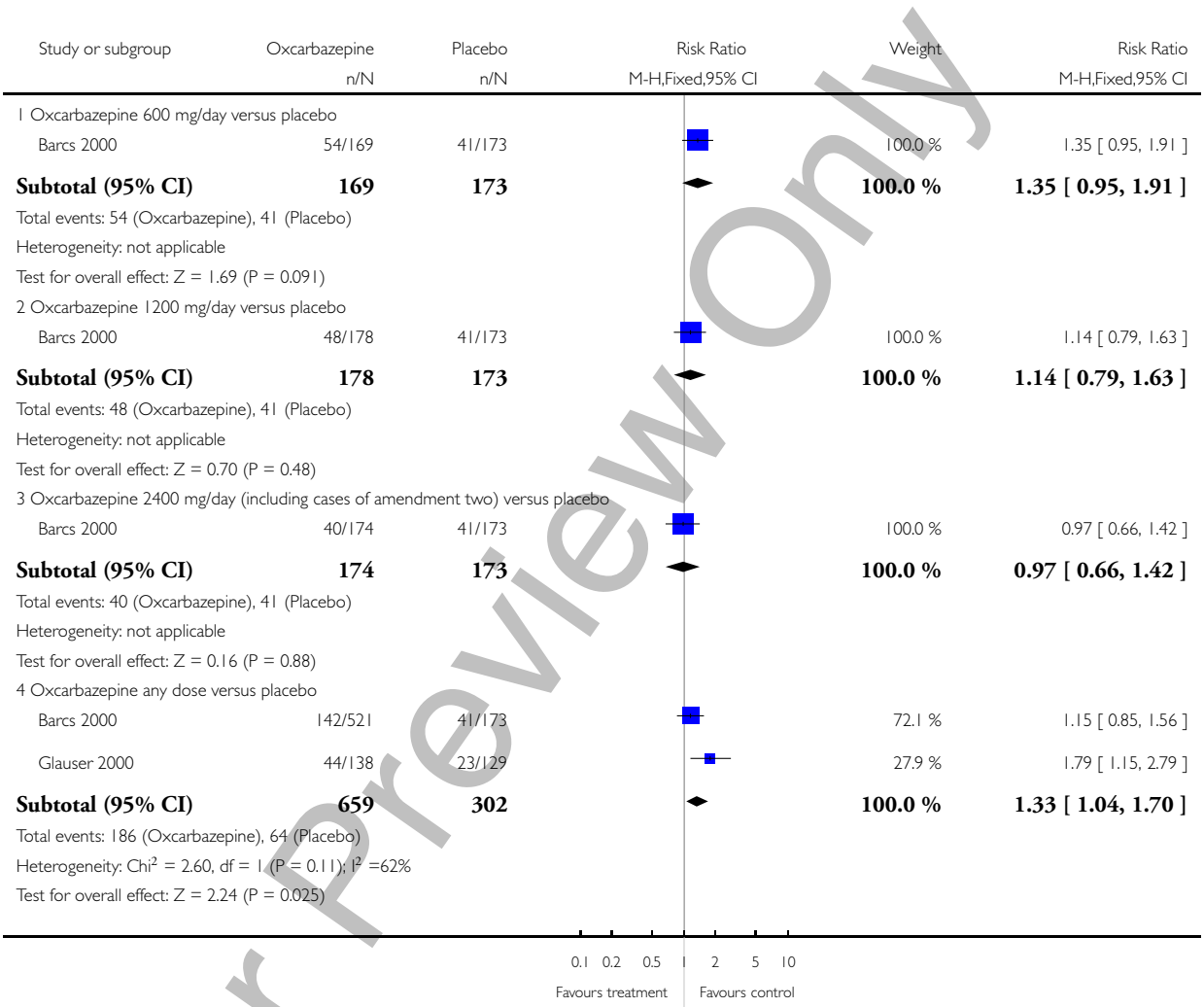


Analysis 3.8. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 8 Headache.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 8 Headache



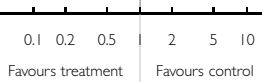
Analysis 3.9. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 9 Hyponatremia.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 9 Hyponatremia

Study or subgroup	Oxcarbazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oxcarbazepine 600 mg/day versus placebo					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Oxcarbazepine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Oxcarbazepine 1200 mg/day versus placebo					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Oxcarbazepine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Oxcarbazepine 2400 mg/day (including cases of amendment two) versus placebo					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Oxcarbazepine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Oxcarbazepine any dose versus placebo					
Barcs 2000	2/519	2/173		100.0 %	0.33 [0.05, 2.35]
Glauser 2000	0/138	0/129			Not estimable
Subtotal (95% CI)	**657**	**302**		**100.0 %**	**0.33 [0.05, 2.35]**
Total events: 2 (Oxcarbazepine), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					

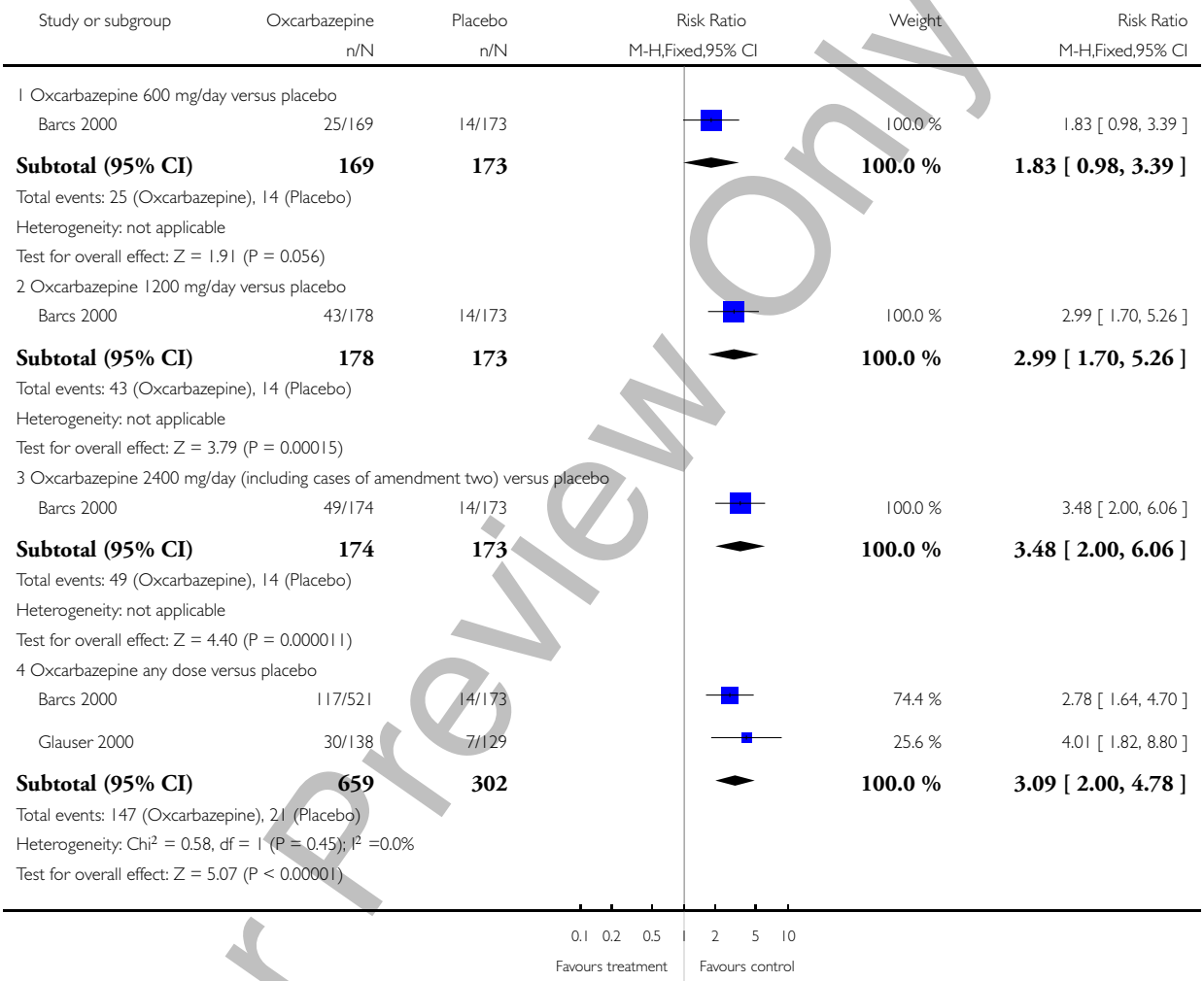


Analysis 3.10. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 10 Nausea.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 10 Nausea

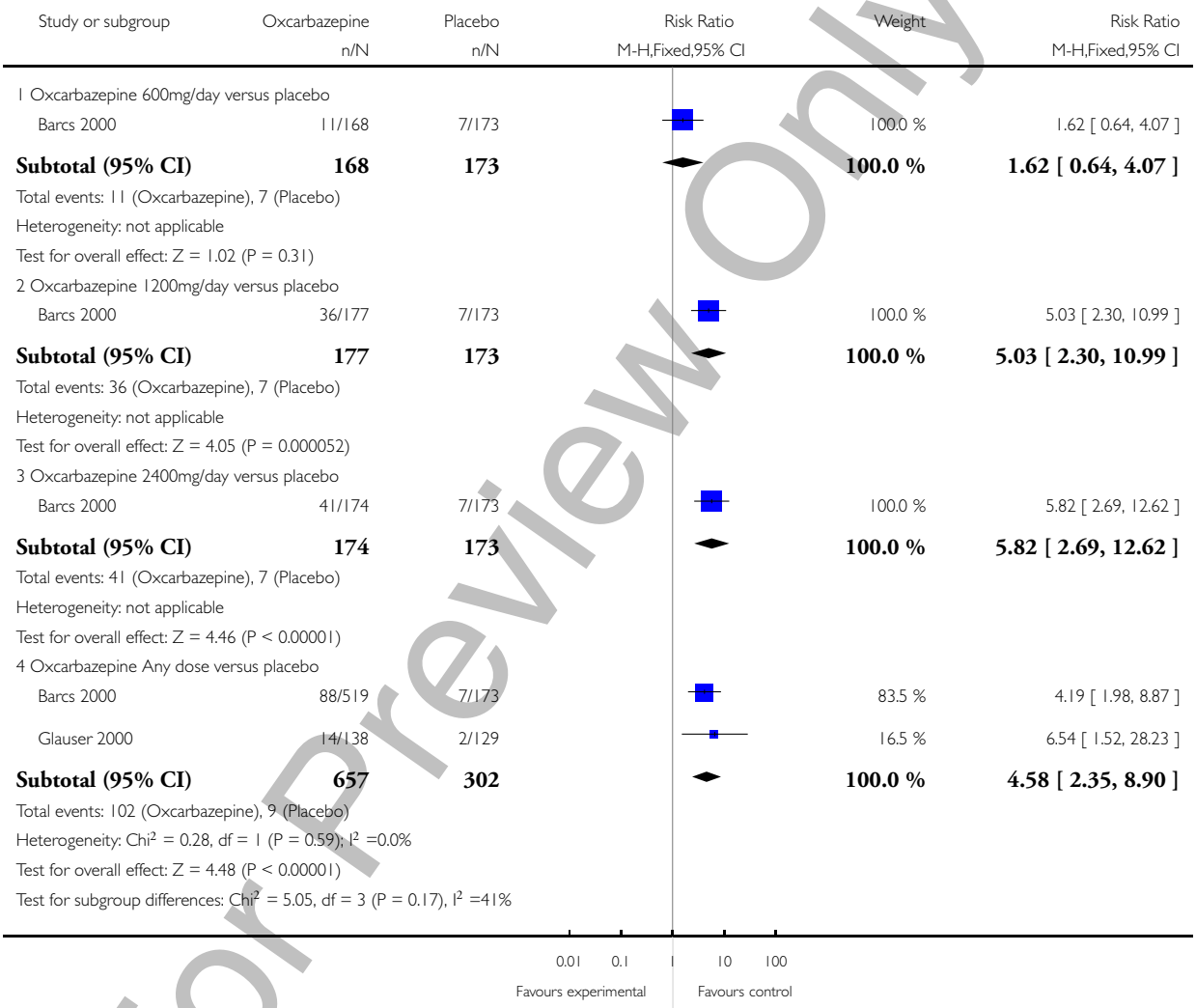


Analysis 3.11. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 11 Nystagmus.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 11 Nystagmus

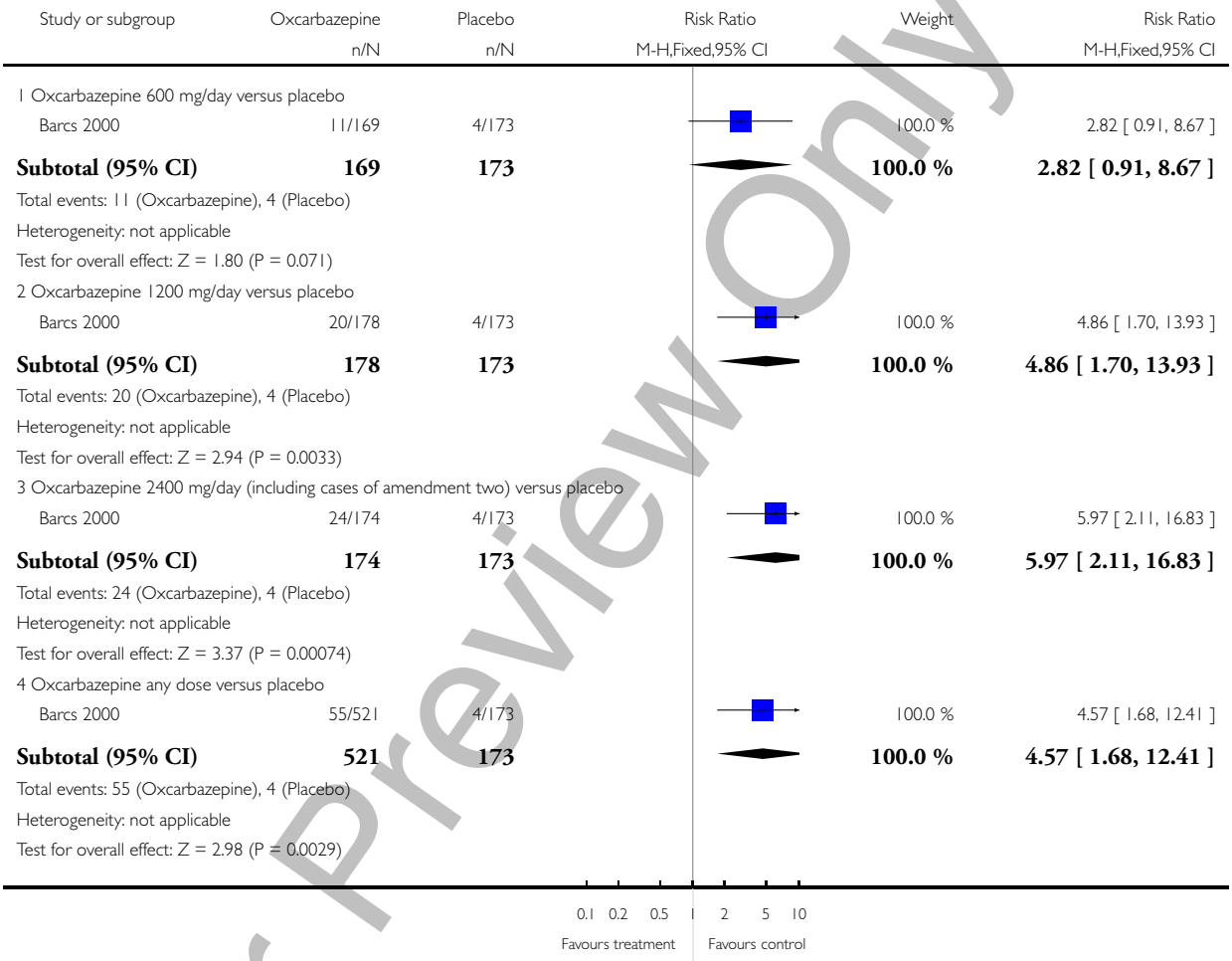


Analysis 3.12. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 12 Vertigo.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 12 Vertigo

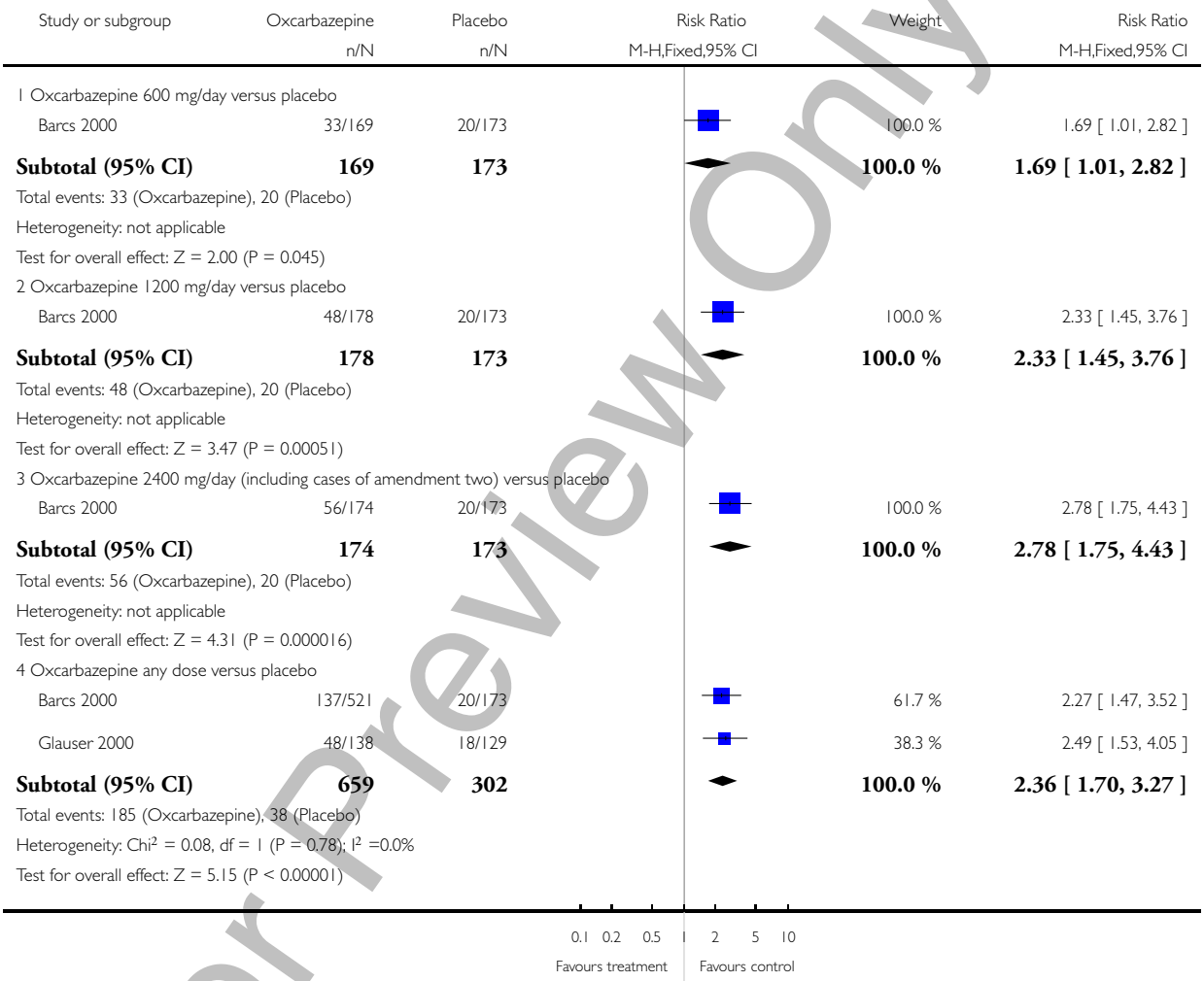


Analysis 3.14. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 14 Somnolence.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 14 Somnolence

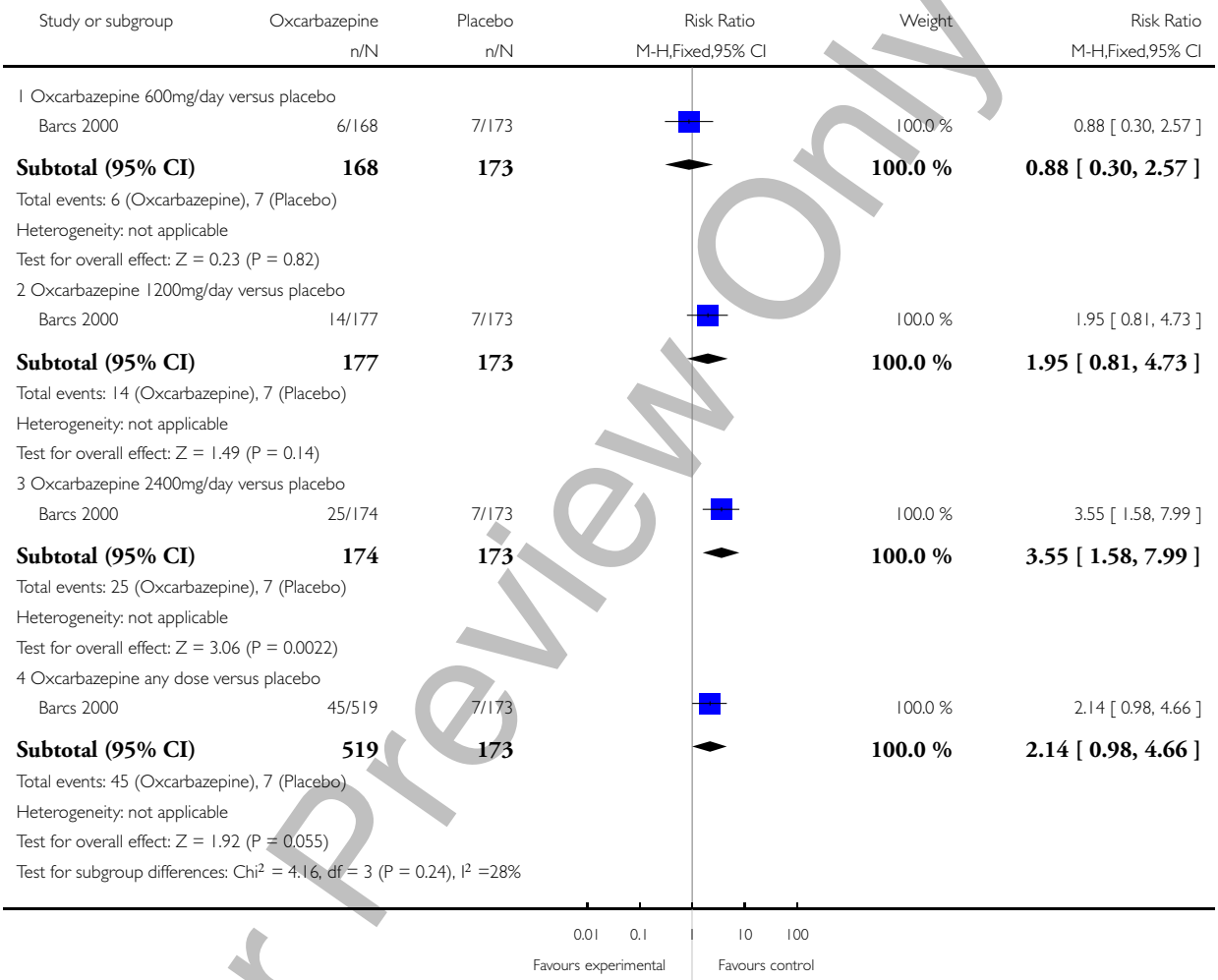


Analysis 3.15. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 15 Tremor.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 15 Tremor

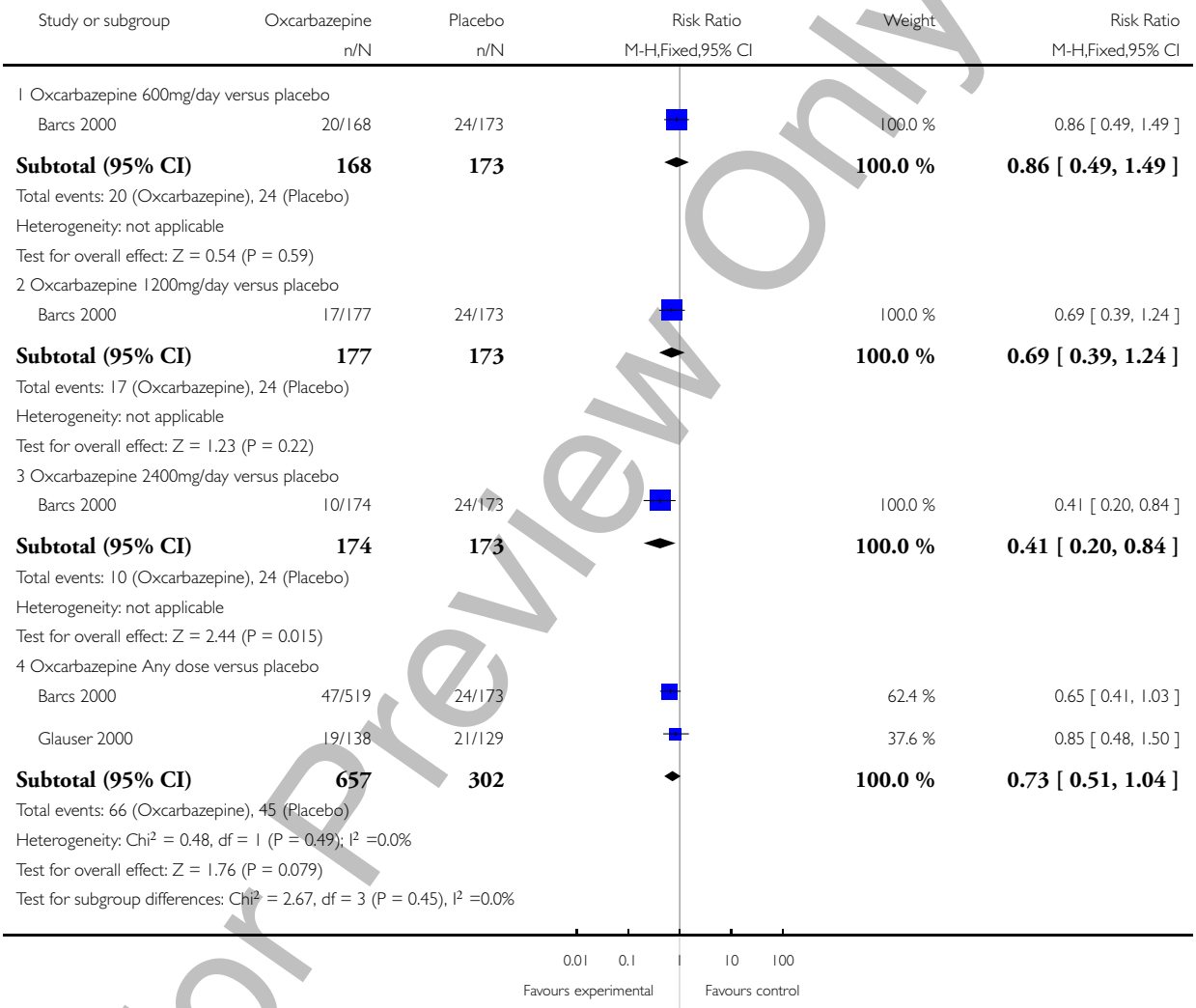


Analysis 3.16. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 16 Viral Infection.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 16 Viral Infection

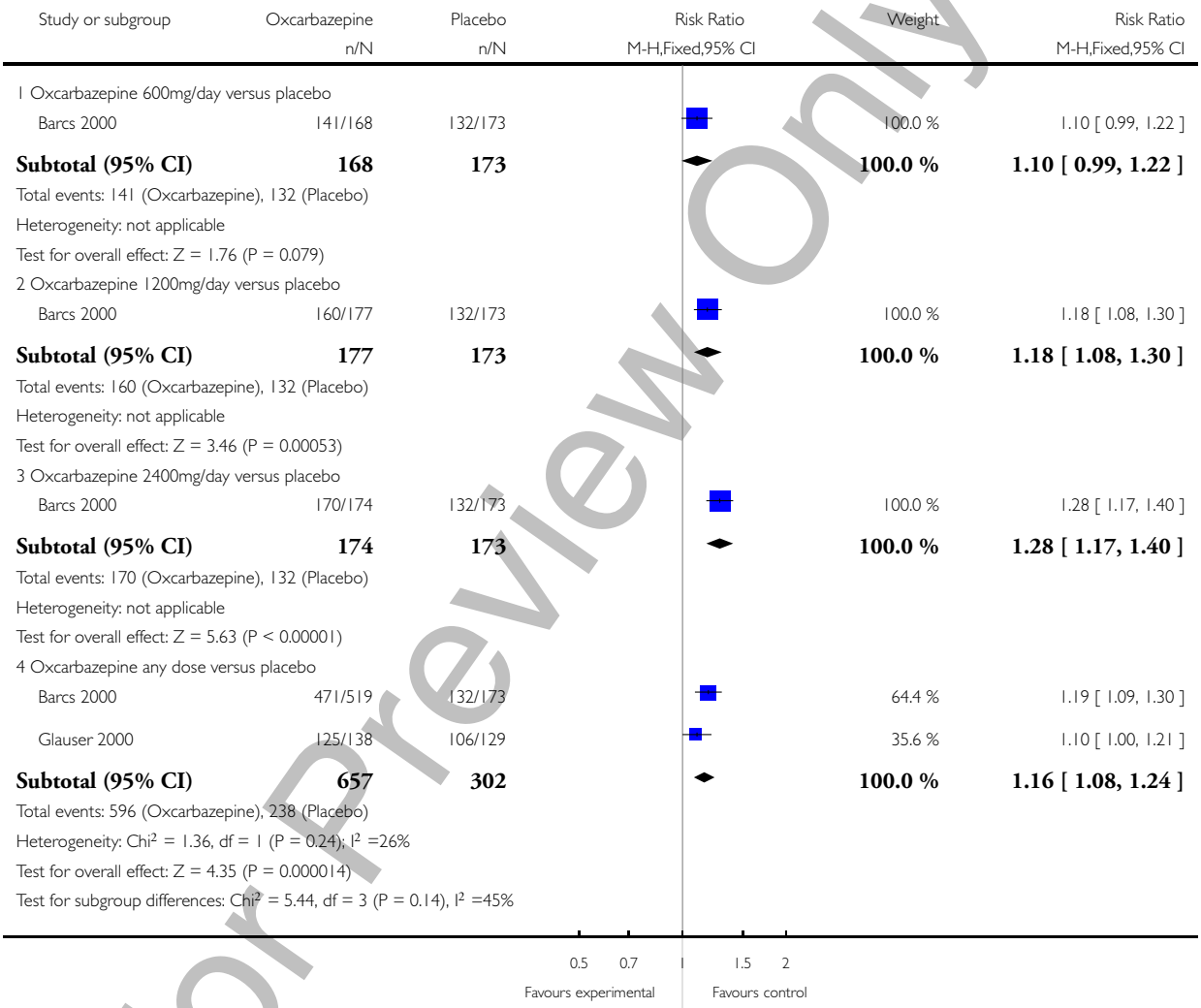


Analysis 3.17. Comparison 3 Side effects of oxcarbazepine in add-on versus placebo, Outcome 17 Any Adverse Event.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 3 Side effects of oxcarbazepine in add-on versus placebo

Outcome: 17 Any Adverse Event



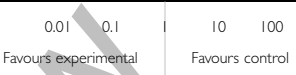
Analysis 4.1. Comparison 4 Efficacy of oxcarbazepine in add-on; high dose versus low dose, Outcome 1 Proportion of responders: The proportion of patients with a 50% or greater reduction in seizure frequency.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 4 Efficacy of oxcarbazepine in add-on; high dose versus low dose

Outcome: 1 Proportion of responders: The proportion of patients with a 50% or greater reduction in seizure frequency

Study or subgroup	Favours experimental n/N	Low Dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	10/19	9/20			1.17 [0.61, 2.23]
Pina-Garza 2005	41/64	30/64			1.37 [0.99, 1.88]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 51 (Favours experimental), 39 (Low Dose)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					



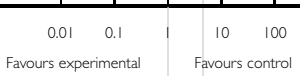
Analysis 5.1. Comparison 5 Global effectiveness of oxcarbazepine in add-on; high dose versus low dose, Outcome 1 Proportion of patients having treatment withdrawn during the course of treatment period.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 5 Global effectiveness of oxcarbazepine in add-on; high dose versus low dose

Outcome: 1 Proportion of patients having treatment withdrawn during the course of treatment period

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	1/19	2/20			0.53 [0.05, 5.34]
Pina-Garza 2005	8/64	5/64			1.60 [0.55, 4.63]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 9 (High dose), 7 (Low dose)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					



Analysis 6.1. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 1 Proprtion of patients having any adverse event.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 1 Proprtion of patients having any adverse event

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	16/19	17/20			0.99 [0.76, 1.30]
Pina-Garza 2005	47/64	26/64			1.81 [1.30, 2.52]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 63 (High dose), 43 (Low dose)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					

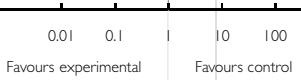
Analysis 6.2. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 2 Infections.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 2 Infections

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pina-Garza 2005	25/64	9/64		100.0 %	2.78 [1.41, 5.48]
Total (95% CI)	**64**	**64**		**100.0 %**	**2.78 [1.41, 5.48]**
Total events: 25 (High dose), 9 (Low dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.95 (P = 0.0032)					
Test for subgroup differences: Not applicable					



Analysis 6.3. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 3 Somnolence.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 3 Somnolence

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	8/19	10/20			0.84 [0.42, 1.67]
Pina-Garza 2005	11/62	3/64			3.78 [1.11, 12.92]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 19 (High dose), 13 (Low dose)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					

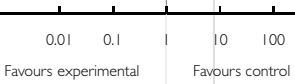
Analysis 6.4. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 4 Ataxia.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 4 Ataxia

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	5/19	7/20		100.0 %	0.75 [0.29, 1.96]
Total (95% CI)	**19**	**20**		**100.0 %**	**0.75 [0.29, 1.96]**
Total events: 5 (High dose), 7 (Low dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

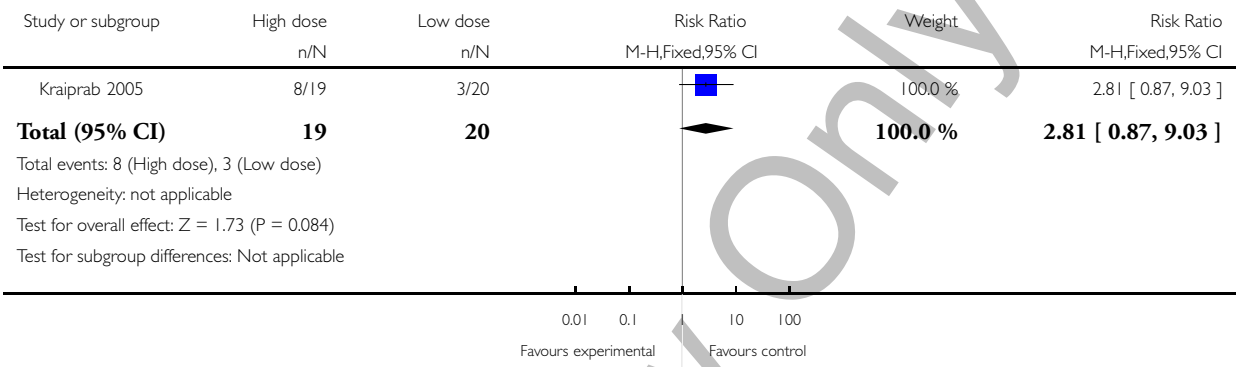


Analysis 6.5. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 5 Dizziness.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 5 Dizziness

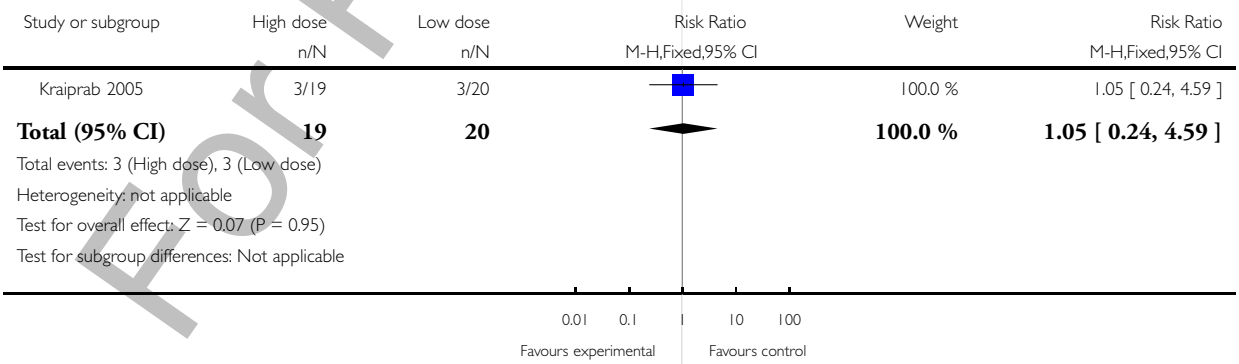


Analysis 6.6. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 6 Headache.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 6 Headache



Analysis 6.7. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 7 Abnormal vision.

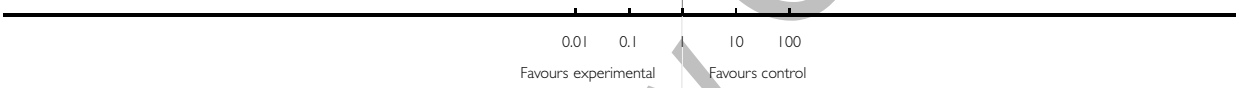
Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 7 Abnormal vision

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	3/19	4/20		100.0 %	0.79 [0.20, 3.07]
Total (95% CI)	**19**	**20**		**100.0 %**	**0.79 [0.20, 3.07]**

Total events: 3 (High dose), 4 (Low dose)
Heterogeneity: not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 8 Diplopia.

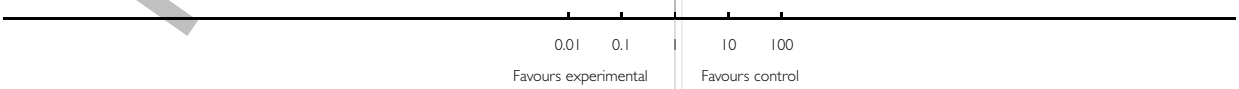
Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 8 Diplopia

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraiprab 2005	1/19	1/20		100.0 %	1.05 [0.07, 15.66]
Total (95% CI)	**19**	**20**		**100.0 %**	**1.05 [0.07, 15.66]**

Total events: 1 (High dose), 1 (Low dose)
Heterogeneity: not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

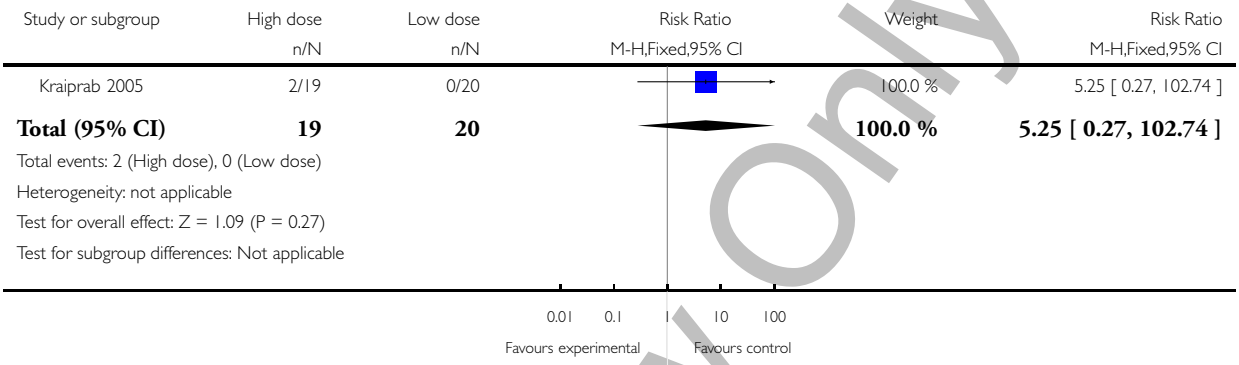


Analysis 6.9. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 9 Vomiting.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 9 Vomiting

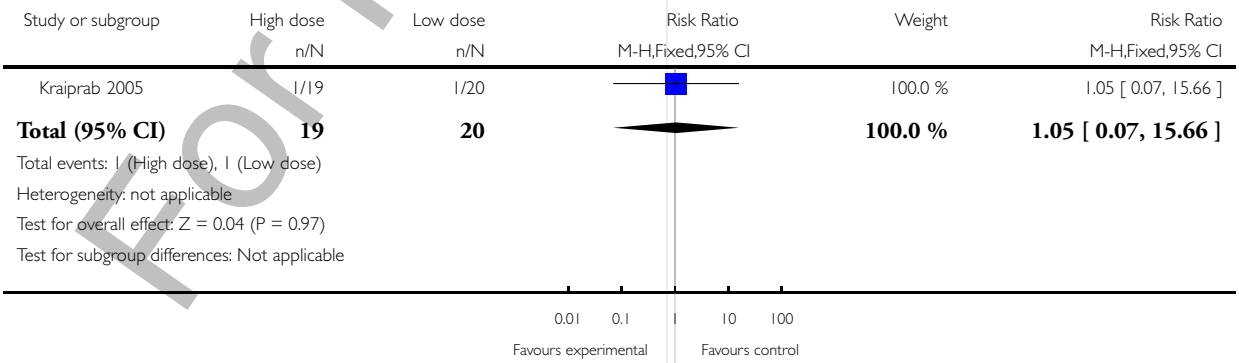


Analysis 6.10. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 10 Nausea.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 10 Nausea

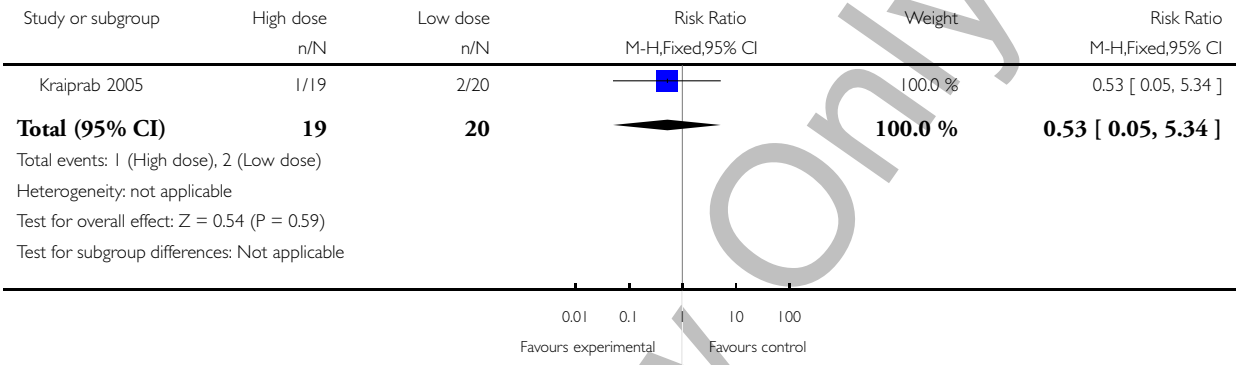


Analysis 6.11. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 11 Fatigue.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 11 Fatigue

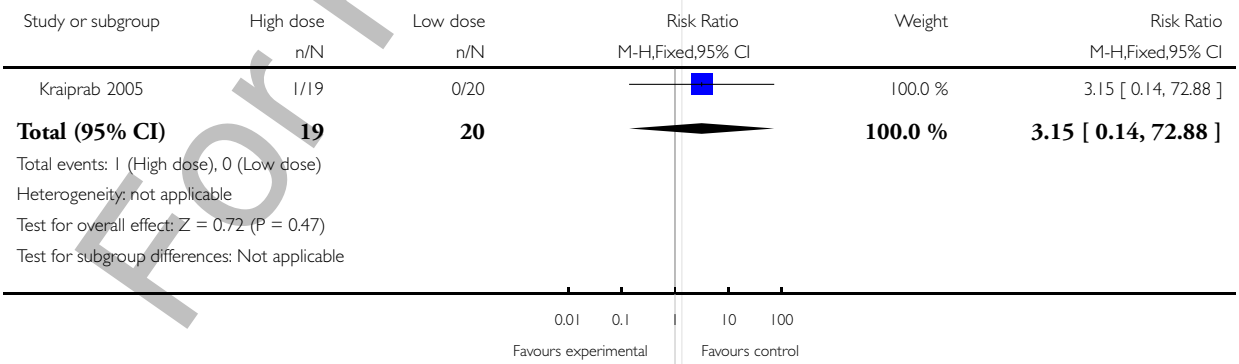


Analysis 6.12. Comparison 6 Side effects of oxcarbazepine in add on; high dose versus low dose, Outcome 12 Rash.

Review: Oxcarbazepine add-on for drug-resistant partial epilepsy

Comparison: 6 Side effects of oxcarbazepine in add on; high dose versus low dose

Outcome: 12 Rash



APPENDICES

Appendix 1. CENTRAL search strategy

#1 (oxcarbazepine or trileptal)
#2 MeSH descriptor Epilepsy explode all trees
#3 MeSH descriptor Seizures explode all trees
#4 epilep* or seizure* or convulsion*
#5 (#2 OR #3 OR #4)
#6 (#1 AND #5)

Appendix 2. MEDLINE search strategy

The following search is based on the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE as set out in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.4, updated March 2005) (Higgins 2005).
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trials/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. 1 or 2 or 3 or 4 or 5 or 6
8. (animals not humans).sh.
9. 7 not 8
10. clinical trial.pt.
11. Clinical Trial/
12. (clin$ adj trial$).ab,ti.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ab,ti.
14. exp PLACEBOS/
15. placebo$.ab,ti.
16. random$.ab,ti.
17. exp Research Design/
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. (animals not humans).sh.
20. 18 not 19
21. 9 or 20
22. epilep$.tw.
23. exp EPILEPSY/
24. seizure$.tw.
25. exp SEIZURES/
26. convulsion$.tw.
27. 22 or 23 or 24 or 25 or 26
28. trileptal.tw.
29. oxcarbazepine.tw.
30. 28 or 29
31. 21 and 27 and 30

WHAT'S NEW

Last assessed as up-to-date: 27 March 2006.

Date	Event	Description
3 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 3, 2000

Date	Event	Description
27 March 2006	Amended	We re-ran our searches on 28 March 2006. One new study (Pina-Garza 2005) has been added to the 'studies awaiting assessment' section. This will be assessed for inclusion in the review at a later date

CONTRIBUTIONS OF AUTHORS

Sergio Castillo and Dieter Schmidt were involved in all stages of the writing of the review. Both review authors independently assessed trials for inclusion and extracted data. Sarah White commented on the draft review. Arif Shukralla and Andrew McKay were involved in selection of studies, extraction of data, analysis if data and producing a draft review.

DECLARATIONS OF INTEREST

Professor Dieter Schmidt has been paid as a consultant and as a speaker for Novartis Pharma.

Lacosamide add-on therapy for partial epilepsy (Review)

Weston J, Shukralla A, McKay AJ, Marson AG

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 7

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[Intervention Review]

Lacosamide add-on therapy for partial epilepsy

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ABSTRACT

Background

Around half of people with epilepsy will not achieve seizure freedom on their first antiepileptic drug, many of whom will require add-on treatment with another drug. Sometimes multiple treatment combinations are tried in order to achieve maximum seizure control, although around a third of people do not achieve complete seizure control. Lacosamide is an antiepileptic drug that has been licensed as an add-on treatment for focal epilepsy.

Objectives

To evaluate the effects of lacosamide when used as add-on treatment for drug-resistant partial epilepsy.

Search methods

We searched the Cochrane Epilepsy Group's Specialised Register (15 October 2013), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to Febuarary 2011), SCOPUS, Clinical Trials.gov and ICTRP. No language restrictions were imposed. We contacted UCB (sponsors of lacosamide) and experts in the field.

Selection criteria

Randomised controlled trials of add-on trials of lacosamide in people with drug-resistant partial epilepsy.

Data collection and analysis

Two authors independently assessed trials for inclusion and extracted the relevant data. The following outcomes were assessed: (i) 50% or greater reduction in seizure frequency; (ii) seizure freedom; (iii) treatment withdrawal for any reason and (iv) adverse events. Primary analyses were intention to treat. Summary risk ratios were estimated for each outcome.

Main results

Three trials were included in our review (1297 participants), which were classified as low risk of bias. All trials were placebo controlled and assessed doses ranging from 200mg to 600mg per day. Trial duration ranged from 24 to 26 weeks. All trials used adequate methods of randomisation and were double blind. Overall the quality of the evidence was rated as high quality. The overall risk ratio for a 50% or greater reduction in seizure frequency for all doses of lacosamide compared to placebo was 1.70 (CI 1.38 to 2.10). The overall risk ratio for seizure freedom for all doses of lacosamide compared to placebo was 2.50 (CI 0.85 to 7.34). The overall risk ratio for treatment

withdrawal for all doses of lacosamide compared to placebo was 1.88 (CI 1.40 to 2.52). Adverse effects which were significantly associated with lacosamide were abnormal coordination RR 6.12 (CI 1.35 to 27.77), blurred vision RR 3.02 (CI 1.19 to 7.68), diplopia RR 5.29 (CI 2.49 to 11.24), dizziness RR 3.53 (CI 2.20 to 5.68), fatigue RR 2.11 (CI 1.12 to 3.97), nausea RR 2.37 (CI 1.23 to 4.58) and vomiting RR 3.10 (CI 1.38 to 6.95). Adverse effects not statistically significant were headache RR 1.35 (CI 0.83 to 2.19), nystagmus RR 1.47 (CI 0.61 to 3.52) and somnolence RR 1.44 (CI 0.81 to 2.57).

Authors' conclusions

This review has shown Lacosamide to be effective well tolerated in the short term when used as an add-on treatment for refractory focal epilepsy in adults. More evidence is needed in children and the longer terms efficacy is unknown.

PLAIN LANGUAGE SUMMARY

The use of Lacosamide in partial epilepsy: does it work and is it harmful?

Background

Lacosamide is an antiepileptic drug which can be added along with others to treat people who have certain types of epileptic seizures. This may be a beneficial drug for people who have taken other antiepileptic medication but have had no success at reducing their seizures. This review looked at how well lacosamide works when added to a patients daily medication and also looked at some of the harms or side effects of the drug.

Participants

To be included in this review all participants had to be adults with a diagnosis of epilepsy, specifically having partial seizures. Patients were required to have been already taking at least two other antiepileptic medications which were not currently working to reduce seizures.

Studies

A search was carried out in October 2013 for all relevant studies. Three trials were included in the review which had a total of 1297 people with epilepsy. All three trials were randomised controlled trials which means the patients were randomly divided into groups and compared. Across all the studies there were five different groups, one group was a placebo group. The patients in this group took medication which was identical to lacosamide in shape and colour but was actually a sugar pill. The other four groups involved taking lacosamide at four different doses.

Results

The review found that lacosamide was good at lowering the amount of seizures the patients experienced. The addition of the antiepileptic drug was over one and a half times better at reducing seizures than the sugar pill. The higher the dose of lacosamide the better it was at reducing the number of seizures. Also patients who took the lacosamide were more likely to have no seizures at all than those who took the sugar pill but they were more likely to end the trial early. This review also looked at side effects of lacosamide and some patients did experience having blurred or double vision, problems with coordination and feeling dizzy, tired and sickly or being sick.

Quality of the Evidence

Altogether the three trials were judged to use good methods and so the evidence in this review was rated as high in quality. More research is need to look at the long term effects of lacosamide and to explore how well it works in children with epilepsy.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lacosamide compared to placebo for partial epilepsy

Patient or population: People with partial epilepsy
Settings: Outpatients
Intervention: Lacosamide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Lacosamide				
50% Reduction in Seizure Frequency - Lacosamide Any dose	**226 per 1000**	**384 per 1000** (311 to 474)	**RR 1.7** (1.38 to 2.1)	1294 (3 studies)	⊕⊕⊕⊕ **high**	
Seizure Freedom - Lacosamide Any dose	**8 per 1000**	**21 per 1000** (7 to 61)	**RR 2.5** (0.85 to 7.34)	1294 (3 studies)	⊕⊕⊕⊕ **high**	
Treatment Withdrawals - Lacosamide any dose	**129 per 1000**	**243 per 1000** (181 to 325)	**RR 1.88** (1.4 to 2.52)	1308 (3 studies)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Epilepsy is a chronic condition often requiring lifelong medical treatment. It predisposes patients to seizures which can lead to physical and psychosocial consequences including depression, social stigma and the inability to drive. The prevalence of active epilepsy is in the order of five to nine per 1000 population (reference). The incidence of epilepsy varies with age from a peak in childhood, declining between the ages of 20 and 50 and increasing after 50. The majority of people diagnosed with epilepsy have their seizures controlled by antiepileptic drugs (AEDs) however up to 20% of patients from population-based studies and up to 30% clinical series will struggle to maintain control over their seizures (Kwan 2000; Reynolds 1981). In order to maximise seizure control patients may require a further AED known as an add-on treatment. Lacosamide is currently licensed as an add-on therapy for focal epilepsy. In this review we assess the efficacy and safety of lacosamide as an add-on therapy for patients with partial epilepsy using both published and unpublished data.

Description of the intervention

Lacosamide is a functional amino acid and was licensed for add-on therapy in 2009 for use with adult patients with partial epilepsy (Chung 2010). Lacosamide has linear kinetics and reaches peak concentrations in plasma in 1 to 4 hours, its half life is 13 hours allowing for twice daily dosing (Doty 2007). Lacosamide is eliminated by renal clearance and does not interact with the P450 system, hence limiting its interaction with the metabolism of other drugs (Kellinghaus 2009). There are no known pharmacodynamic interactions with lacosamide. In clinical practice, lacosamide is started at 100 mg a day in divided doses, to a maximum of 400 mg a day until seizure freedom or reduction in seizure frequency is achieved. The current formulations of lacosamide include a tablet, oral syrup or intravenous form. Lacosamide is available in 50mg, 100mg 150mg and 200 mg doses. The maximum licensed dose is currently 400 mg per day.

How the intervention might work

The drug works by enhancing the inactivation of slow sodium channels.This is a novel mechanism of action as the traditional AEDs act on inactivation of fast sodium channels thus lacosamide selectively affects pathological currents caused by slow channels versus inactivation of fast channels which occurs in normally functioning neurons. This prevents the activation of synaptic currents thereby preventing the formation of pathological currents from propagating and thus stabilising the neural network (Doty 2007). As an add-on therapy the drug is used in conjunction with standard therapy to help achieve freedom from seizures.

Why it is important to do this review

Current published randomised controlled trials have outlined the efficacy and safety of lacosamide as an add-on therapy in adult patients with partial epilepsy. There are several alternatives currently available for adjunctive therapy in adults and a systematic review would inform clinicians better regarding efficacy and safety. Lacosamide has recently been launched in the UK and this review will inform clinicians of its efficacy and summarise data on the adverse effects of it's use.

OBJECTIVES

To evaluate the efficacy and tolerability of lacosamide when used as an add-on treatment for patients with drug-resistant partial epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies which met the following criteria:
(1) Randomised controlled trials (RCTs);
(2) Double or single blinded studies;
(3) Placebo controlled, active controlled studies or studies using range of dose as controls;
(4) Add-on studies with a minimum treatment period of 8 weeks.

Types of participants

People of any age with drug-resistant partial epilepsy (i.e. experiencing simple partial, complex partial or secondary generalised tonic-clonic seizures).

Types of interventions

(1) The active treatment group received treatment with lacosamide in addition to their usual AED treatment.
(2) The control group received a placebo or another AED in addition to their usual AED treatment.

Types of outcome measures

Primary outcomes

50% or greater reduction in seizure frequency

The primary outcome is the proportion of people with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period. This outcome was chosen as it is commonly reported in this type of study and can also be calculated for studies that do not report it, provided that baseline seizure data were available.

Secondary outcomes

Seizure freedom

The proportion of people with complete cessation of seizures during the treatment period.

Treatment withdrawal

The proportion of people having treatment withdrawn during the course of the treatment period as a measure of global effectiveness. Treatment is likely to be withdrawn due to adverse effects, lack of efficacy or a combination of both, and this is an outcome to which the individual makes a direct contribution. In trials of short duration it is likely that adverse effects will be the most common reason for withdrawal.

Adverse Effects

The proportion of people experiencing the following adverse effects:

1. ataxia;
2. concentration impairment;
3. dizziness;
4. headache;
5. fatigue;
6. nausea/vomiting;
7. paraesthesias;
8. somnolence;
9. speech difficulties;
10. thinking abnormally;
11. weight loss/decrease.

The adverse effects were chosen as authors considered them to be common and important adverse effects of other similarly prescribed AEDs.

Quality of life

The difference in quality of life scores between groups measured using a standardised measure.

Cognitive changes

The difference in cognition scores between groups measured using a standardised measure.

Search methods for identification of studies

Electronic searches

We searched the following databases:-

1. The Cochrane Epilepsy Group's Specialized Register (15/10/2013) see Appendix 1;
2. The Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 9) (*The Cochrane Library, October 2013*) Appendix 2;
3. MEDLINE (Ovid) (1946 to October 2013) see Appendix 3;
4. SCOPUS (1823 to 2013) see Appendix 4;
5. Clinical Trials.gov; and
6. ICTRP.

We did not impose any date or language restrictions.

Searching other resources

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

We contacted the manufacturers of lacosamide and experts in the field for information about any unpublished or ongoing studies. We define unpublished data as trial data obtained from manufacturers that is not reported or obtained from peer reviewed journals. Other sources will include conference abstracts and posters.

Data collection and analysis

Selection of studies

Two authors (JP and AS) independently assessed trials for inclusion. Any disagreements were resolved by discussion with another author (AGM). Three review authors (JP, AS, AJM) extracted data and assessed risk of bias; any disagreements were resolved by discussion.

Data extraction and management

We extracted the following information for each trial using a data extraction form:

Methodological/trial design

- Method of randomisation and allocation concealment.
- Method of blinding.
- Missing participants.
- Length of baseline period.
- Length of treatment period.
- Dose(s) of lacosamide used.

Patient/demographic information

- Total number of participants allocated to each treatment group.

- Age/gender.
- Seizure types.
- Seizure frequency during baseline period.
- Number of background AEDs.

Outcomes

We recorded the number of people experiencing each outcome (see Types of outcome measures) per randomised group. We contacted trial authors for any missing information.

Assessment of risk of bias in included studies

Two review authors independently made an assessment of risk of bias for each trial using Cochrane 'Risk of bias' tables as described in (Higgins 2011). We rated included studies as high, low or unclear on six domains applicable to randomised controlled trials: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias. We created a 'Summary of findings' table and employed the GRADE approach for assessing quality of evidence.

Measures of treatment effect

The majority of outcomes are categorical and results are presented as risk ratios with 95% confidence intervals. For the quality of life measures, scores and statistics from scales used are summarised in tables and text.

Dealing with missing data

All analyses were undertaken according to the principal of intention to treat. When data were missing from trial reports, additional data was requested from trialists and trial sponsors. We also planned sensitivity analysis to determine the effect missing data on results.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing participant and trial characteristics across trials. Factors included age, seizure type, number of AEDs taken at time of randomisation, trial design and duration.

We assessed statistical heterogeneity using the I^2 test, with a value of greater than 75% indicating significant heterogeneity. Provided no statistical heterogeneity was found (P>0.10), we synthesised the results using a fixed-effect model. In the event that heterogeneity was found, we planned to use a random-effects model using the inverse variance method.

Assessment of reporting biases

We assessed the potential for outcome reporting bias using the Outcome Reporting Bias in Trials (ORBIT) tool (Kirkham 2010).

Data synthesis

We employed a fixed-effect model meta-analysis to synthesise the data. comparisons we expected to carry out included:

1. intervention group versus controls of seizure reduction;
2. intervention group versus controls on seizure freedom;
3. intervention group versus controls on treatment withdrawal;
4. intervention group versus controls on adverse effects
5. intervention group versus controls on quality of life;
6. intervention group versus controls on cognition.

Each comparison was stratified by type of control group, that is placebo or active control, and study characteristics to ensure the appropriate combination of study data.

For the primary outcome our preferred estimator was the Mantel-Haenszel risk ratio (RR). For the majority of outcomes we used 95% confidence intervals (CIs). For individual adverse effects we used 99% CIs to make allowance for multiple testing. Our analyses included all participants in the treatment group to which they had been allocated.

Subgroup analysis and investigation of heterogeneity

Other than analyses assessing dose effects, no subgroup analyses were planned in this review.

Sensitivity analysis

Sensitivity analyses were planned to assess the impact of missing data, but this was not necessary.

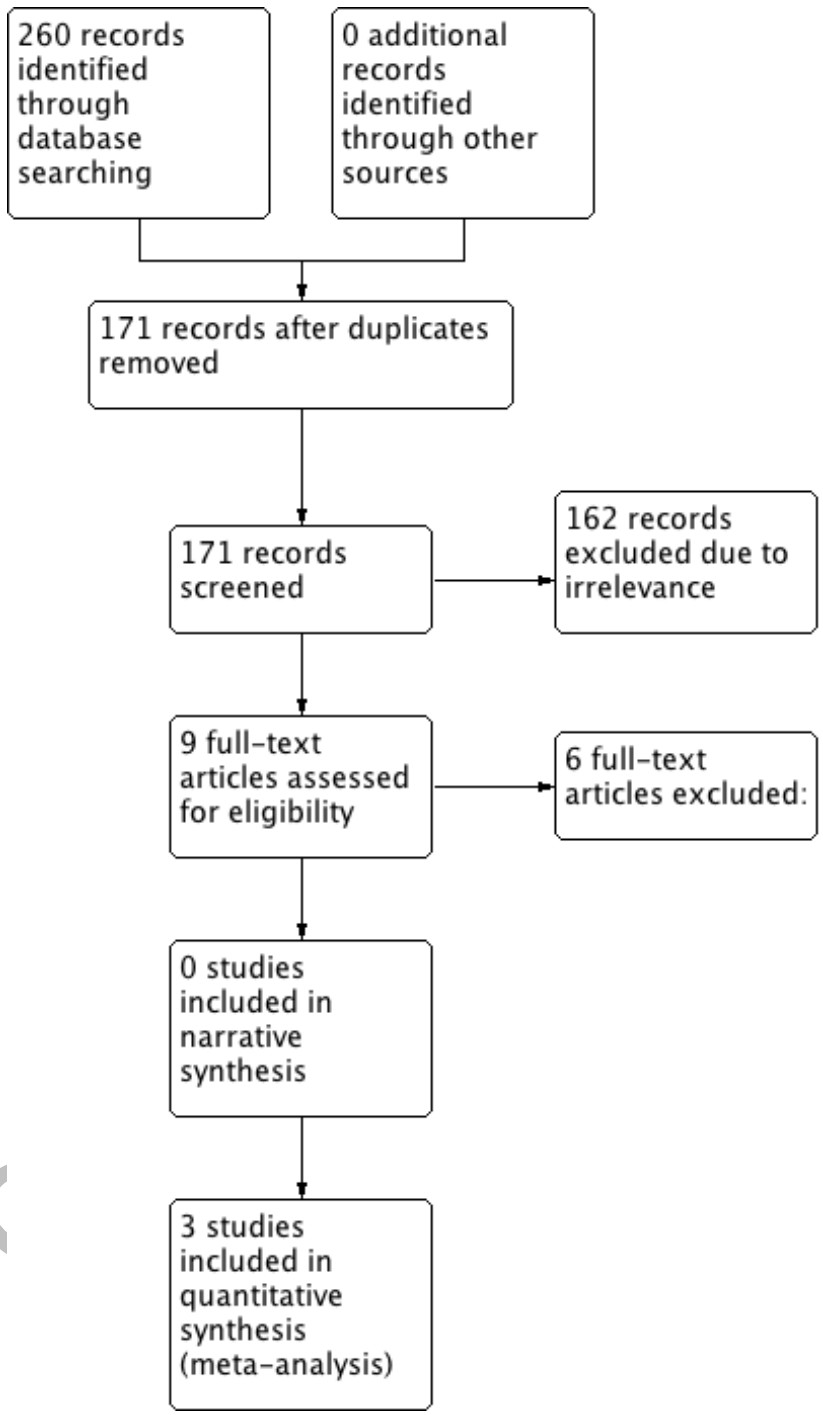
RESULTS

Description of studies

Results of the search

The search revealed 260 records from the databases outlined in Electronic searches. After duplicates (89) were removed, 171 records remained and were screened for inclusion in the review. At this point 162 records were excluded due to irrelevance leaving 9 full texts to be assessed for eligibility. Folowing this we excluded 6 studies (see Figure 1 and Characteristics of excluded studies for reasons for exclusion). A total of three studies were included in the review, all of which were included in meta-analysis.

Figure 1. Study flow diagram.



Included studies

Overall three RCTs examining lacosamide in comparison to a placebo are included in this review (Ben Menachem 2007; Halasz 2009; Chung 2010). All three trials were undertaken as part of a drug development programme and were sponsored by UCB Pharma. The first was a Phase IIb study (Ben Menachem 2007), while the other two (Halasz 2009; Chung 2010) were phase III studies. A total of 1311 patients were randomised; 270 patients were allocated to 200 mg of lacosamide; 471 patients were allocated to 400 mg of lacosamide; 366 patients were allocated to 600 mg of lacosamide and 190 patients were allocated to placebo. In all trials participants recruited were currently experiencing either simple or complex partial seizures with or without secondary generalised seizures and were previously taking a minimum of two AED treatments.

Ben Menachem 2007 was a multicentre (58 centres worldwide) double-blind, parallel trial with a baseline period of 8 weeks, titration phase of 6 weeks and treatment period of 12 weeks. There were fours arms to the trial: lacosamide 200 mg per day (n=107), lacosamide 400 mg per day (n=108), lacosamide 600 mg per day (n=106) and placebo (n=86). Tablets were administered in a twice daily fashion. Outcomes investigated included seizure frequency, seizure freedom, quality of life and adverse events. The impact of dose was also examined.

Chung 2010 was a multi-centre (US) double-blind, parallel trial with a baseline period of 8 weeks, followed by a 6-week titration period and a 12-week treatment period. This was a three armed trial: lacosamide 400 mg per day (n=204), lacosamide 600 mg daily (n=97) and placebo (n=104). Outcomes reported were seizure frequency, seizure freedom, withdrawals, and adverse events.

Halasz 2009 was an international multi-centre double-blind parallel trial with a baseline period of 8 weeks, a titration phase of 4 weeks and a treatment period of 12 weeks. Patients were randomised to one of three groups: lacosamide 200 mg daily (n= 163), lacosamide 400 mg daily (n=159) or placebo (n=163). The outcomes investigated were seizure frequency and freedom, withdrawals and adverse events.

For more details of each trial ands for a complete list of all outcomes investigated see Characteristics of included studies.

Excluded studies

We excluded one trial comparing two rates of intravenous infusion of lacosamide and further comparison of oral versus intravenous formation. This trial was excluded as this trial did not include a placebo group**.** Another trial was excluded as it compared the pharmacokinetic interaction of lacosamide to carbamazepine. Four other trials were published comparing lacosamide and placebo in patients with diabetic neuropathy and hence were beyond the scope of this review.

Risk of bias in included studies

All three studies however were funded by industry to acquire a licence this would introduce an element of bias. Our analysis of risk of bias deemed that one out of the three studies (Ben Menachem 2007) was superior to the other two in alleviating bias. Our analysis using the ORBIT tool however showed that two trials did conduct quality of life measures but they were not published in the trial report. Instead these results were published separately.

Allocation

All three trials adequately use methods to ensure lack of bias in sequence generation and allocation concealment. This was done via an interactive voice response service (IVRS) and the randomisation schedule was pre-determined by a computer generated program using generated pseudo-random numbers. Clinical investigators had no way of finding out allocated medication unless the patient was unblinded during the study.

Blinding

Blinding was ensured by identical tablets and packaging in all three trials included.

Incomplete outcome data

There were no patients for which outcomes were incompletely reported. There were significant number of patients in the three trials that were screen or randomisation failures. These were not considered to contribute to incomplete outcomes.

Selective reporting

Ben Menachem 2007 reported all outcomes planned in the methods section. Halasz 2009 and Chung 2010 did not report quality of life outcomes in trial reports but these were reported at conference proceedings and poster presentations. A judgement would need to be made if reporting of outcomes as a separate publication would be considered as selective reporting. We have deemed that this does not constitute as selective reporting. Accidental injury as an adverse event was not reported in the unpublished data but was reported in the published trial reports. We included this outcome in our analysis.

Other potential sources of bias

All three trials were funded by the pharmaceutical industry and to date there are no non-industry funded studies. This bias was reduced however by requesting unpublished data from trial sponsors.

Effects of interventions

See: **Summary of findings for the main comparison** Lacosamide compared to placebo for partial epilepsy

Lacosamide versus placebo

50% reduction in seizure frequency

Data from all three studies contributed to this outcome and the following two outcomes. Across all doses no clinical or statistical heterogeneity was found (I^2=5%). A Chi^2 test for heterogeneity was non-significant (P<0.00001). The overall risk ratio (RR) for any dose lacosamide compared to placebo is 1.70 (95% CI 1.38 to 2.10). For lacosamide 200 mg the RR is 1.41 (95% CI 1.07 to 1.85), for lacosamide 400 mg the RR is 1.80 (95% CI 1.43 to 2.25), and for lacosamide 600 mg the overall RR is 1.98 (95% CI 1.43 to 2.73). Increased doses were found to increase the likelihood of patients responding to lacosamide.

Seizure Freedom

We found no clinical or statistical heterogeneity across any dose lacosamide (I^2=0%), a Chi^2 test was also non-significant (P=0.47). The overall RR for any dose lacosamide compared to placebo is 2.50 (95% CI 0.85 to 7.34). For lacosamide 200 mg the RR is 1.81 (95% CI 0.50 to 6.57), for lacosamide 400 mg the RR is 2.70 (95% CI 0.85 to 8.56), and for lacosamide 600 mg the RR is 7.09 (95% CI 0.90 to 55.70). Increased doses of lacosamide were found to increase the likelihood of patients becoming seizure free.

Treatment Withdrawal

We found no clinical or statistical heterogeneity across any dose lacosamide (I^2=16%), a Chi^2 test was also non-significant (P=0.31). The overall RR for any dose lacosamide compared to placebo is 1.88 (95% CI 1.40 to 2.52. For lacosamide 200 mg the RR is 1.43 (95% CI 0.95 to 2.15), for lacosamide 400 mg the RR is 1.79 (95% CI 1.31 to 2.46), and for lacosamide 600 mg the RR is 3.04 (95% CI 2.02 to 4.59). Increased doses of lacosamide were found to increase the likelihood of patients withdrawing from the trials.

Quality of life measures

Quality of life was reported in one trial (Ben Menachem 2007), the other two studies recorded the QOLIE-31, Seizure Severity Scale (SSS) and Patient Global Impression of Change scale (PGIC) measures but they were not reported in the published version. We were able to view the poster presentations of these results which contained pooled analyses of these outcomes. Key outcomes analysed were the QOLIE-31, the SSS and the PGIC. The QOLIE-31 provides a range of sores in various epilepsy specific measures and is not amenable to meta analysis. However the PGIC is a change of numbers of patients entering or leaving a defined quality of life state which would be amenable to analysis if results were made available. We can state in this review that quality of life did improve in patients who experienced either seizure freedom or a significant reduction in seizure frequency.

Adverse Effects

Meta-analysis was able to be performed on 10 adverse effects. Lacosamide was significantly associated with: abnormal coordination RR 6.12 (99% CI 1.35 to 27.77), blurred vision RR 3.02 (99% CI 1.19 to 7.68), diplopia RR 5.29 (99% CI 2.49 to 11.24), dizziness RR 3.53 (99% CI 2.20 to 5.68), fatigue RR 2.11 (99% CI 1.12 to 3.97), nausea RR 2.37 (99% CI 1.23 to 4.58), and vomiting RR 3.10 (99% CI 1.38 to 6.95). Non-significant findings for adverse effects included: headache RR 1.35 (99% CI 0.83 to 2.19), nystagmus RR 1.47 (99% CI 0.61 to 3.52) and somnolence RR 1.44 (99% CI 0.81 to 2.57).

Serious Adverse Events

Any dose lacosamide was associated with serious adverse events RR 1.78 (99% CI 0.85 to 3.73). Higher doses were found to be less associated with serious adverse events: lacosamide 200 mg RR 2.00 (99% CI 0.80 to 5.00), lacosamide 400 mg RR 1.97 (99% CI 0.88 to 4.40) and lacosamide 600 mg RR 0.74 (99% CI 0.19 to 2.86).

DISCUSSION

Summary of main results

Our results have demonstrated the efficacy and safety of lacosamide in reducing seizure frequency using the responder rate as an outcome measure. Two studies did not find the 200 mg dose to be efficacious compared to placebo but our meta-analysis showed a marginal superiority over placebo which was statistically significant. The clinical implications are that patients need not be titrated up to a higher or medium dose range for lacosamide to work. Adverse events are more common at the higher doses hence a low dose that is found to be efficacious with less probability of adverse events is desirable. Our results also show that lacosamide is efficacious at 400 mg and 600 mg at reducing seizure frequency compared to placebo this was suggested in previous studies.

There was no statistically significant difference between treatment and control with regard to seizure freedom. This was due to the small number of patients who did become seizure free and the short duration of the maintenance period for this outcome. Depite this result it is worth noting that the small number of patients who were seizure free were having frequent seizures after having failed on poly therapy previously. There is however no further clinical details given on this subgroup of patients regarding their duration of illness compared to the rest of the cohort.

Lacosamide 200 mg per day compared to placebo was tolerated well with no significant difference between proportion of patients withdrawing for any reason. Tolerablity of the 400 mg dose compared to placebo was less and the summary statistic suggests that patients are almost two times as likely to withdraw for any reason compared to placebo. Tolerability of the 600 mg doser was poorer still with patients three times a likely to withdraw for any reason. The adverse events profile of lacosamide shown here and in the published reports suggest that adverse events are common and are likely to occur at increasingly higher doses. Adverse events that were significantly more with lacosamide compared to placebo are; vomiting, vertigo, nausea, fatigue, dizziness, diplopia, coordination abnormal, blurred vision and ataxia. Only vertigo, dizziness and diplopia were significantly more likely compared to placebo using the 200 mg dose.

Two trials showed no increase in serious adverse events in the treatment groups compared to placebo (Chung 2010; Ben Menachem 2007) but was significantly greater in Halasz 2009.

Overall lacosamide is a novel treatment for epilepsy with efficacy at low, medium and high doses. Lacosmide is tolerated well at low to medium doses but not at high dose. Some patients after having tried standard AEDs for epilepsy have become seizure free with lacosamide.

Overall completeness and applicability of evidence

The evidence presented here highlights the efficacy and safety of lacosamide compared to placebo. The three studies have reported efficacy and safety data to allow a credible review, however quality of life measures (PGIC and SSS) are incompletely and poorly reported in two studies (Halasz 2009 and Chung 2010). This data was not available from the sponsors in the unpublished repots. Futher studies are needed to refine the data presented here.

Quality of the evidence

The trials used in our analyses were of high quality with most of the outcomes reported. We were able to get further details of outcomes form the trial sponsors. Key primary and secondary outcomes were reported well in both published and unpublished reports. We however had to clarify with the trial sponsors on details of allocation concealments and allocation sequence generation. We listed the bias for this as low in risk of bias tables as we received clarification from trial sponsors. The published reports however did not report sequence generation for Ben Menachem 2007 and Chung 2010. Allocation concealment was not reported in the three published trials.

AUTHORS' CONCLUSIONS

Implications for practice

We conclude that lacosamide is efficacious, and tolerable at 200 mg per day with the possibility of having fewer adverse events, this does not mean that the treatment effect size of this dose has changed from that reported in clinical trials but meta-analysis has shown that this effect is real and the implications are that a less that 400mg dose is effective with the chance of fewer side effects.

Implications for research

We conclude that further studies are need to be conducted to add to the body of evidence presented here.

ACKNOWLEDGEMENTS

We would like to thank UCB Pharma for providing unpublished data.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ben Menachem 2007

Methods	Phase IIb, multicentre, multinational, randomised, double-blinded, parallel-group, placebo-controlled, dose-response trial Four treatment groups: Placebo, Lacosamide 200 mg, Lacosamide 400 mg and Lacosamide 600 mg Baseline period: 8 weeks Titration period: 6 weeks (titration rate of 100mg per week until target dose) Treatment period:12 weeks ITT was defined as the proportion of patients who received one dose of trial drug and who produced one seizure diary entry Safety population was defined as all randomised patients who took one dose of trial medication
Participants	Adults aged 18 to 65 Simple or complex partial seizures for at least two years having being uncontrolled on at least two AEDs Concomitant allowed drugs were a stable dose regimen of 1 or 2 AEDs with or without VNS. Approximately 84% of patients were taking at least 2 AEDs with the rest taking 1 8 weeks prior to the baseline period and during the 8-week baseline period, patients must have had at least 4 partial-onset seizures per 28-days on average, with no seizure-free period longer than 21 days The numbers of patients in each treatment group had roughly equal numbers. Age, sex and ethnicity are similar in each arm with most patients being Caucasian (93%)
Interventions	Placebo Lacosamide 200 mg/day Lacosamide 400 mg/day Lacosamide 600 mg/day 82% of patients achieved target dose
Outcomes	This list includes all outcomes reported in the published study: Change in seizure frequency per 28 days from baseline analyses in both the ITT and PP populations Responder rate defined as the proportion of patients with a 50% reduction in seizure frequency in both the ITT and PP populations. Also, 75% responder rate Proportion of patients experiencing a 25% increase in seizure frequency Percentage change in seizure frequency Achievement of seizure-free status Proprtion of patients seizure free throughout the 12 week maintenance period Percentage change in seizure free days compared to baseline Change in median of QOLIE 31 scores compared to baseline Proprtion of patients showing a CGIC change from baseline to “very much improved” or “much improved” Adverse Events (adverse events reported above a threshold of 5%) Proprtion of patients meeting target dose Proportion of patients having dose reduction due to adverse events

	Proprtion of patients discontinued due to adverse events Proportion of patients with Serious Adverse Events Pharmacokinetic outcomes
Notes	Five hundred and forty two patients were screened, and 421 were randomised into the four groups. Three patients were not included in the safety or efficacy populations because site audit findings suggested site protocol non-compliance (treatment allocations not indicated in trial paper) and a further three were excluded from the ITT population due to not having any post-baseline efficacy measurements. Thus 415 are included in the efficacy analyses. AEs that occurred in at least 5% of patients are shown in the trial paper Accident (Not otherwise specified) (NOS) is one AE outcome reported in the published paper but was not reported in the unpublished data provided by the study sponsors. This outcome was included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was carried out centrally by the trial sponsor. This was done via an automated voice response system. Randomisation list was made by a random number generator. Patients were randomly allocated to either Lacosamide or placebo
Allocation concealment (selection bias)	Low risk	Clinical investigators were blinded to treatment allocated centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	All placebo and Lacosamide tablets and their accompanying packaging (blister cards, boxes) were identical in appearance (size and colour)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome of seizure frequency was carried out by patients and assessors who were blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no patients with incomplete outcomes
Selective reporting (reporting bias)	Low risk	For further information see ORBIT tool below

Chung 2010

Methods	Phase III, randomised, multicentre, double-blinded, parallel-group, placebo-controlled trial Patients were allocated in a 1:2:1 ratio to Placebo, Lacosamide 400 mg and Lacosamide 600 mg Baseline period:8 weeks Titration period: 6 weeks (titration rate of 100mg per week till target dose) Treatment period: 12 weeks ITT was defined as the proportion of patients who received one dose of trial drug and who produced one seizure diary entry Safety population was defined as all randomised patients who took one dose of trial medication
Participants	Adults aged 16 to 70 years Simple or complex partial seizures documented on EEG and either MRI or CT scan consistent with diagnosis of epilepsy Patients would need to have a two year history of intractable epilepsy and have perilously failed two AEDs During the 8-week baseline period, patients must have had at least 4 partial-onset seizures per 28-days on average, with no seizure-free period longer than 21 days Patients would need to be on a stable dose regimen of 1 to 3 AEDs with or without VNS. Approximately 27% of patients were taking 3 AEDs, 55% taking 2 AEDs and 18% taking 1 AED. Approximately 37% of patients were taking 3 AEDs, 50% taking 2 AEDs and 13% taking 1 AED This study had a higher proportion of non-Caucasian population (18.5%) compared to Ben Menachem 2007 (7%)
Interventions	Placebo Lacosamide 400 mg Lacosamide 600 mg 81.1% of patients achieved target dose
Outcomes	This list includes all outcomes reported in the published study: Change in seizure frequency per 28 days from baseline analyses in both the ITT and PP populations Change rate defined as the proportion of patients with a 50% reduction in seizure frequency in both the ITT and PP populations. Also, 75% responder rate Reduction in seizure frequency per 28 days from baseline and the 50% responder rate were also categorised by seizure type. Subgroups were; all seizure types; secondary generalised tonic clonic seizures; complex partial seizures and simple partial seizures Percentage change in seizure frequency per 28 days from baseline to maintenance period Number and proportion of patients with seizure-free status during the maintenance period calculated in an ITT method Percentage of seizure-free days throughout maintenance period Adverse Events (adverse events reported above a threshold of 10%) Proprion of patients withdrawing from adverse event Pharmocokinetic outcomes Atlhough quality of life outcomes were conducted they are not reported in the final published report

Notes	151 patients were screen failures: 67 at initial screening prior to the 8-week baseline phase and 84 at the end of the 8-week baseline phase screened prior to randomisation. AEs that occurred in at least 10% of patients are shown in the trial paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central pre-determined computer generated (pseudo-random number generated) randomisation schedule, via IVRS, was used. The investigator (or his/her name designee) called the IVRS on the toll-free number provided. The IVRS asked the investigator to identify the subject by confirming the subject initials and his/her date of birth. The investigator was required to confirm that the subject fulfilled all inclusion criteria and none of the exclusion criteria, and that the subject had provided written informed consent. A randomisation number was assigned by the IVRS
Allocation concealment (selection bias)	Low risk	Clinical investigators were blinded to treatment allocated centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	All placebo and Lacosamide tablets and their accompanying packaging (blister cards, boxes) were identical in appearance (size and colour)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome of seizure frequency was carried out by patients and assessors who were blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcomes. Adverse events were reported above a 10% threshold compared to the other two reports which reported AEs above or equal to 5%
Selective reporting (reporting bias)	Low risk	All outcomes stipulated in the published article were reported but conference abstracts and posters pertaining to this study repotted quality of life outcomes that were pub-

		lished separately. For further information see ORBIT tool below

Halasz 2009

Methods	Phase III, randomised, multicentre, double-blinded, parallel-group, placebo-controlled trial Patients were allocated in a 1:1:1 ratio to Placebo, Lacosamide 200 mg and Lacosamide 400 mg Baseline period: 8 weeks Titration period: 4 weeks (titration rate of 100mg per week till target dose) Treatment period: 12 weeks ITT was defined as the proportion of patients who received one dose of trial drug and who produced one seizure diary entry Safety population was defined as all randomised patients who took one dose of trial medication
Participants	Adults aged 16 to 70 years Simple or complex partial seizures documented on EEG and either MRI or CT scan consistent with diagnosis of epilepsy Patients would need to have a two year history of intractable epilepsy and have perilously failed two AEDs During the 8-week baseline period, patients must have had at least 4 partial-onset seizures per 28-days on average, with no seizure-free period longer than 21 days Patients would need to be on a stable dose regimen of 1 to 3 AEDs with or without VNS. Approximately 27% of patients were taking 3 AEDs, 55% taking 2 AEDs and 18% taking 1 AED Patients were predominantly Caucasian (99%)
Interventions	Placebo Lacosamide 200 mg Lacosamide 400 mg
Outcomes	This list includes all items reported in this study Change in seizure frequency per 28 days from baseline analyses in both the ITT and PP populations Responder rate defined as the proportion of patients with a 50% reduction in seizure frequency in both the ITT and PP populations Percentage change in seizure frequency per 28 days from baseline to maintenance period Proprtion of patients seizure free Proportion of seizure free days Withdrawals due to any reason and due to Adverse Events Adverse Events. (Adverse events reported above a threshold of 5%) Serious Adverse Events Pharmacokientic outcomes
Notes	Thirty eight patients were excluded after screening and 61 patients were not randomised. AEs that occurred in at least 5% of patients are shown in the trial paper
Risk of bias	

Halasz 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central pre-determined computer generated (pseudo-random number generated) randomisation schedule, via IVRS, was used. The investigator (or his/her named designee) called the IVRS on the toll-free number provided. The IVRS asked the investigator to identify the subject by confirming the subject initials, subject number, and his/her date of birth. The investigator was required to confirm that the subject fulfilled all inclusion criteria and none of the exclusion criteria, and that the subject had provided written informed consent. A randomisation number was assigned by the IVRS
Allocation concealment (selection bias)	Low risk	Clinical investigators were blinded to treatment allocated centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	All placebo and LCM tablets and their accompanying packaging were identical in appearance (size and colour) and packaging so that neither the investigator nor the subject was able to tell whether the trial medication was active or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome of seizure frequency was carried out by patients and assessors who were blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcomes were reported
Selective reporting (reporting bias)	Low risk	All outcomes stipulated in the published article were reported but conference abstracts and posters pertaining to this study repotted quality of life outcomes that were published separately. For further information see ORBIT tool below

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Biton 2005	See Biton 2008
Biton 2008	This study compared intravenous lacosamide and oral lacosamide and could not be used in the current review as there was no placebo group. This study might be used if future data becomes available
Jatuzis 2005	Pharmacokinetic study
Jatuzis 2006	Pharmacokinetic study
Kalvianinen 2007	Pharmacokinetic study
Rosenfeld 2005	Pharmacokinetic study

DATA AND ANALYSES

Comparison 1. Lacosamide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% Reduction in Seizure Frequency	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Lacosamide 200 mg	2	522	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.07, 1.85]
1.2 Lacosamide 400 mg	3	825	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.43, 2.25]
1.3 Lacosamide 600 mg	2	402	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.43, 2.73]
1.4 Lacosamide Any dose	3	1294	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.38, 2.10]
2 Seizure Freedom	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Lacosamide 200 mg/day	2	522	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.50, 6.57]
2.2 Lacosamide 400 mg/day	3	825	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [0.85, 8.56]
2.3 Lacosamide 600 mg/day	2	402	Risk Ratio (M-H, Fixed, 95% CI)	7.09 [0.90, 55.70]
2.4 Lacosamide Any dose	3	1294	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.85, 7.34]
3 Treatment Withdrawals	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.95, 2.15]
3.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.31, 2.46]
3.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [2.02, 4.59]
3.4 Lacosamide any dose	3	1308	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.40, 2.52]
4 Abnormal Coordination	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
4.1 Lacosamide 200 mg	1	326	Risk Ratio (M-H, Fixed, 99% CI)	7.0 [0.45, 108.28]
4.2 Lacosamide 400 mg	2	630	Risk Ratio (M-H, Fixed, 99% CI)	6.13 [1.34, 28.07]
4.3 Lacosamide 600 mg	1	201	Risk Ratio (M-H, Fixed, 99% CI)	5.90 [0.84, 41.30]
4.4 Lacosamide Any dose	2	890	Risk Ratio (M-H, Fixed, 99% CI)	6.12 [1.35, 27.77]
5 Accident NOS	1		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
5.1 Lacosamide 200 mg	1	204	Risk Ratio (M-H, Fixed, 99% CI)	1.13 [0.45, 2.87]
5.2 Lacosamide 400 mg	1	205	Risk Ratio (M-H, Fixed, 99% CI)	0.45 [0.13, 1.55]
5.3 Lacosamide 600 mg	1	203	Risk Ratio (M-H, Fixed, 99% CI)	0.38 [0.10, 1.43]
5.4 Lacosamide Any dose	1	418	Risk Ratio (M-H, Fixed, 99% CI)	0.65 [0.28, 1.53]
6 Ataxia	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Lacosamide 200 mg	2	204	Risk Ratio (M-H, Fixed, 99% CI)	1.21 [0.17, 8.36]
6.2 Lacosamide 400 mg	2	205	Risk Ratio (M-H, Fixed, 99% CI)	4.19 [0.85, 20.73]
6.3 Lacosamide 600 mg	1	203	Risk Ratio (M-H, Fixed, 99% CI)	7.32 [1.58, 33.99]
6.4 Lacosamide Any dose	3	418	Risk Ratio (M-H, Fixed, 99% CI)	4.23 [0.93, 19.15]
7 Blurred Vision	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 Lacosamide 200 mg	1	204	Risk Ratio (M-H, Fixed, 99% CI)	0.73 [0.13, 3.93]
7.2 Lacosamide 400 mg	2	513	Risk Ratio (M-H, Fixed, 99% CI)	2.91 [1.06, 7.98]
7.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	4.38 [1.66, 11.57]
7.4 Lacosamide Any dose	2	823	Risk Ratio (M-H, Fixed, 99% CI)	3.02 [1.19, 7.68]
8 Diplopia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 95% CI)	4.10 [1.41, 11.95]
8.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [2.40, 11.18]
8.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 95% CI)	6.61 [2.63, 16.61]
8.4 Lacosamide Any dose	3	1308	Risk Ratio (M-H, Fixed, 95% CI)	5.29 [2.49, 11.24]
9 Dizziness	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
9.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 99% CI)	2.26 [1.14, 4.46]
9.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 99% CI)	3.33 [2.02, 5.50]

9.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	5.04 [2.88, 8.82]
9.4 Lacosamide Any dose	3	1308	Risk Ratio (M-H, Fixed, 99% CI)	3.53 [2.20, 5.68]
10 Fatigue	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.80, 3.38]
10.2 Lacosamide 400 mg	2	527	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.00, 4.03]
10.3 Lacosamide 600 mg	1	203	Risk Ratio (M-H, Fixed, 95% CI)	3.84 [1.51, 9.80]
10.4 Lacosamide Any dose	2	903	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.12, 3.97]
11 Headache	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
11.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 99% CI)	1.37 [0.68, 2.75]
11.2 Lacosamide 400 mg	3	837	Risk Ratio (M-H, Fixed, 99% CI)	1.50 [0.89, 2.51]
11.3 Lacosamide 600 mg	2	406	Risk Ratio (M-H, Fixed, 99% CI)	1.09 [0.54, 2.21]
11.4 Lacosamide Any dose	3	1310	Risk Ratio (M-H, Fixed, 99% CI)	1.35 [0.83, 2.19]
12 Proportion of patients with Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Lacosamide 200 mg	1	326	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.47, 3.76]
12.2 Lacosamide 400 mg	1	322	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.64, 4.59]
12.3 Lacosamide Any dose	1	485	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.61, 3.75]
13 Nausea	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
13.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 99% CI)	1.70 [0.67, 4.29]
13.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 99% CI)	2.46 [1.21, 5.01]
13.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	2.44 [1.13, 5.26]
13.4 Lacosamide Any Dose	3	1308	Risk Ratio (M-H, Fixed, 99% CI)	2.37 [1.23, 4.58]
14 Nystagmus	2		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
14.1 Lacosamide 200 mg	1	204	Risk Ratio (M-H, Fixed, 99% CI)	0.54 [0.09, 3.45]
14.2 Lacosamide 400 mg	2	513	Risk Ratio (M-H, Fixed, 99% CI)	1.31 [0.49, 3.51]
14.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	2.08 [0.80, 5.40]
14.4 Lacosamide Any dose	2	823	Risk Ratio (M-H, Fixed, 99% CI)	1.47 [0.61, 3.52]
15 Peripheral Edema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Lacosamide 200 mg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Lacosamide 400 mg	1	308	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.12, 52.86]
15.3 Lacosamide 600 mg	1	201	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.13, 77.97]
15.4 Lacosamide Any dose	1	405	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.13, 46.73]
16 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Lacosamide 200 mg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Lacosamide 400 mg	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.36, 3.64]
16.3 Lacosamide 600 mg	1	201	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.03, 2.36]
16.4 Lacosamide Any dose	1	405	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.28, 2.70]
17 Somnolence	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Lacosamide 200 mg	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.43, 3.36]
17.2 Lacosamide 400 mg	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.92, 3.14]
17.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.60, 2.46]
17.4 Lacosamide Any dose	2	823	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.81, 2.57]
18 Tremor	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Lacosamide 200 mg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Lacosamide 400 mg	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.55, 2.67]
18.3 Lacosamide 600 mg	1	201	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.82, 4.27]
18.4 Lacosamide Any dose	1	405	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 2.99]
19 Upper Respiratory Tract Infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Lacosamide 200 mg	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.46, 2.14]
19.2 Lacosamide 400 mg	1	205	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.50, 2.26]
19.3 Lacosamide 600 mg	1	203	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.19, 1.30]

19.4 Lacosamide Any dose	1	418	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.44, 1.63]
20 Vertigo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Lacosamide 200 mg	1	326	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [1.04, 12.90]
20.2 Lacosamide 400 mg	1	322	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [0.96, 12.19]
20.3 Lcaosamide 600 mg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Lacosamide Any dose	1	485	Risk Ratio (M-H, Fixed, 95% CI)	3.54 [1.07, 11.71]
21 Vomiting	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
21.1 Lacosamide 200 mg	2	530	Risk Ratio (M-H, Fixed, 99% CI)	2.52 [0.75, 8.47]
21.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 99% CI)	2.95 [1.27, 6.85]
21.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	3.64 [1.34, 9.87]
21.4 Lacosamide Any dose	3	1308	Risk Ratio (M-H, Fixed, 99% CI)	3.10 [1.38, 6.95]
22 Serious Adverse Events	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
22.1 Lacosmaide 200 mg	2	530	Risk Ratio (M-H, Fixed, 99% CI)	2.00 [0.80, 5.00]
22.2 Lacosamide 400 mg	3	835	Risk Ratio (M-H, Fixed, 99% CI)	1.97 [0.88, 4.40]
22.3 Lacosamide 600 mg	2	404	Risk Ratio (M-H, Fixed, 99% CI)	0.74 [0.19, 2.86]
22.4 Lacosamide Any dose	3	1308	Risk Ratio (M-H, Fixed, 99% CI)	1.78 [0.85, 3.73]

Analysis 1.1. Comparison 1 Lacosamide versus placebo, Outcome 1 50% Reduction in Seizure Frequency.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 1 50% Reduction in Seizure Frequency

Study or subgroup	Favours Placebo n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Lacosamide 200 mg					
Ben Menachem 2007	35/107	21/96		35.0 %	1.50 [0.94, 2.38]
Halasz 2009	56/160	41/159		65.0 %	1.36 [0.97, 1.90]
Subtotal (95% CI)	**267**	**255**		**100.0 %**	**1.41 [1.07, 1.85]**
Total events: 91 (Favours Placebo), 62 (Placebo)					
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 2.44 (P = 0.015)					
2 Lacosamide 400 mg					
Ben Menachem 2007	44/107	21/96		25.1 %	1.88 [1.21, 2.92]
Chung 2010	77/201	19/104		28.4 %	2.10 [1.35, 3.26]
Halasz 2009	64/158	41/159		46.4 %	1.57 [1.14, 2.17]
Subtotal (95% CI)	**466**	**359**		**100.0 %**	**1.80 [1.43, 2.25]**
Total events: 185 (Favours Placebo), 81 (Placebo)					
Heterogeneity: Chi^2 = 1.17, df = 2 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 5.09 (P < 0.00001)					
3 Lacosamide 600 mg					

(*Continued* . . .)

(. . . *Continued*)

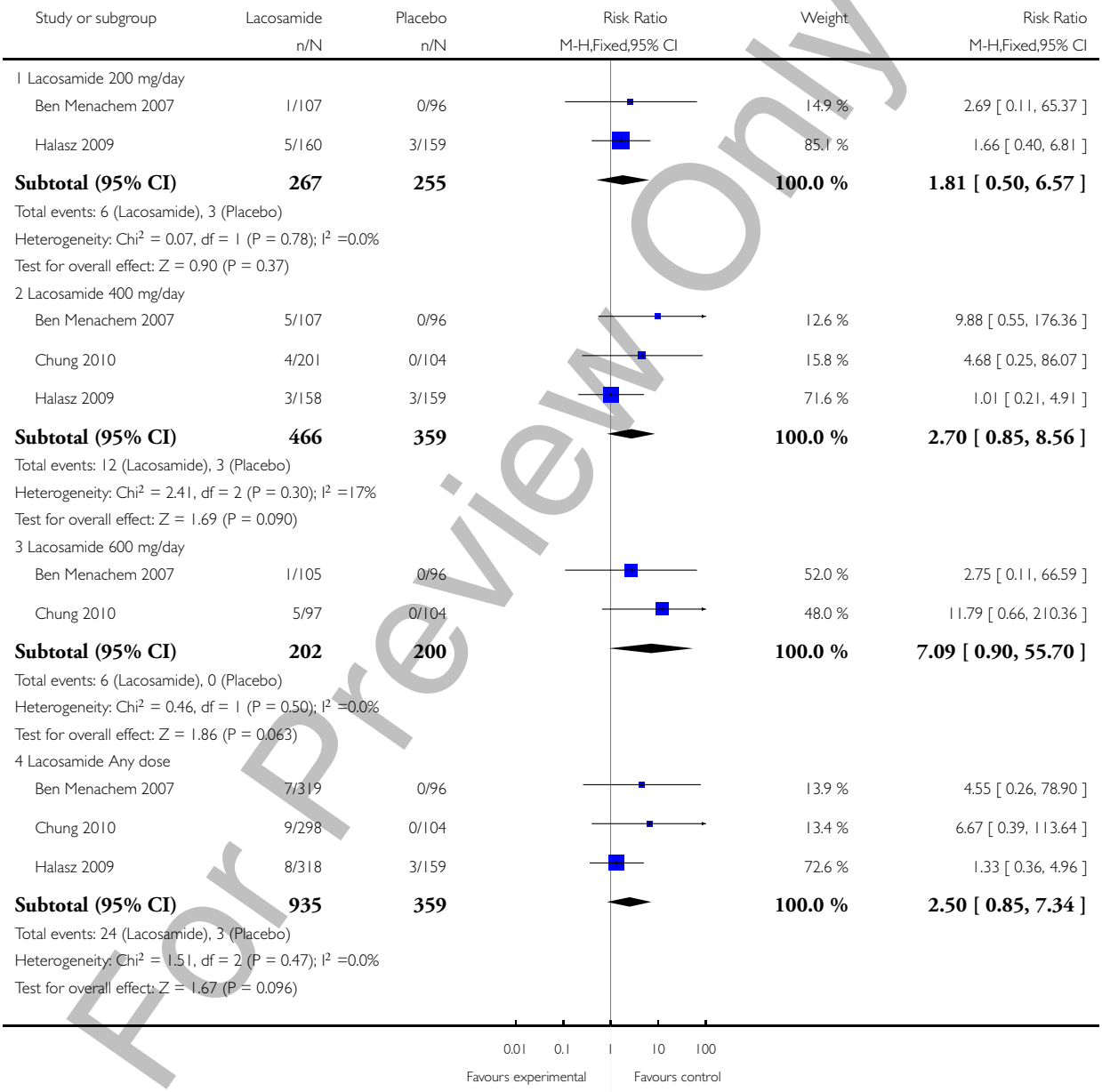
Study or subgroup	Favours Placebo n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ben Menachem 2007	40/105	21/96		54.5 %	1.74 [1.11, 2.73]
Chung 2010	40/97	19/104		45.5 %	2.26 [1.41, 3.61]
Subtotal (95% CI)	**202**	**200**		**100.0 %**	**1.98 [1.43, 2.73]**
Total events: 80 (Favours Placebo), 40 (Placebo)					
Heterogeneity: Chi^2 = 0.61, df = 1 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 4.11 (P = 0.000039)					
4 Lacosamide Any dose					
Ben Menachem 2007	119/319	21/96		28.0 %	1.71 [1.14, 2.55]
Chung 2010	117/298	19/104		24.5 %	2.15 [1.40, 3.30]
Halasz 2009	120/318	41/159		47.5 %	1.46 [1.09, 1.97]
Subtotal (95% CI)	**935**	**359**		**100.0 %**	**1.70 [1.38, 2.10]**
Total events: 356 (Favours Placebo), 81 (Placebo)					
Heterogeneity: Chi^2 = 2.10, df = 2 (P = 0.35); I^2 =5%					
Test for overall effect: Z = 4.94 (P < 0.00001)					

Analysis 1.2. Comparison 1 Lacosamide versus placebo, Outcome 2 Seizure Freedom.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 2 Seizure Freedom

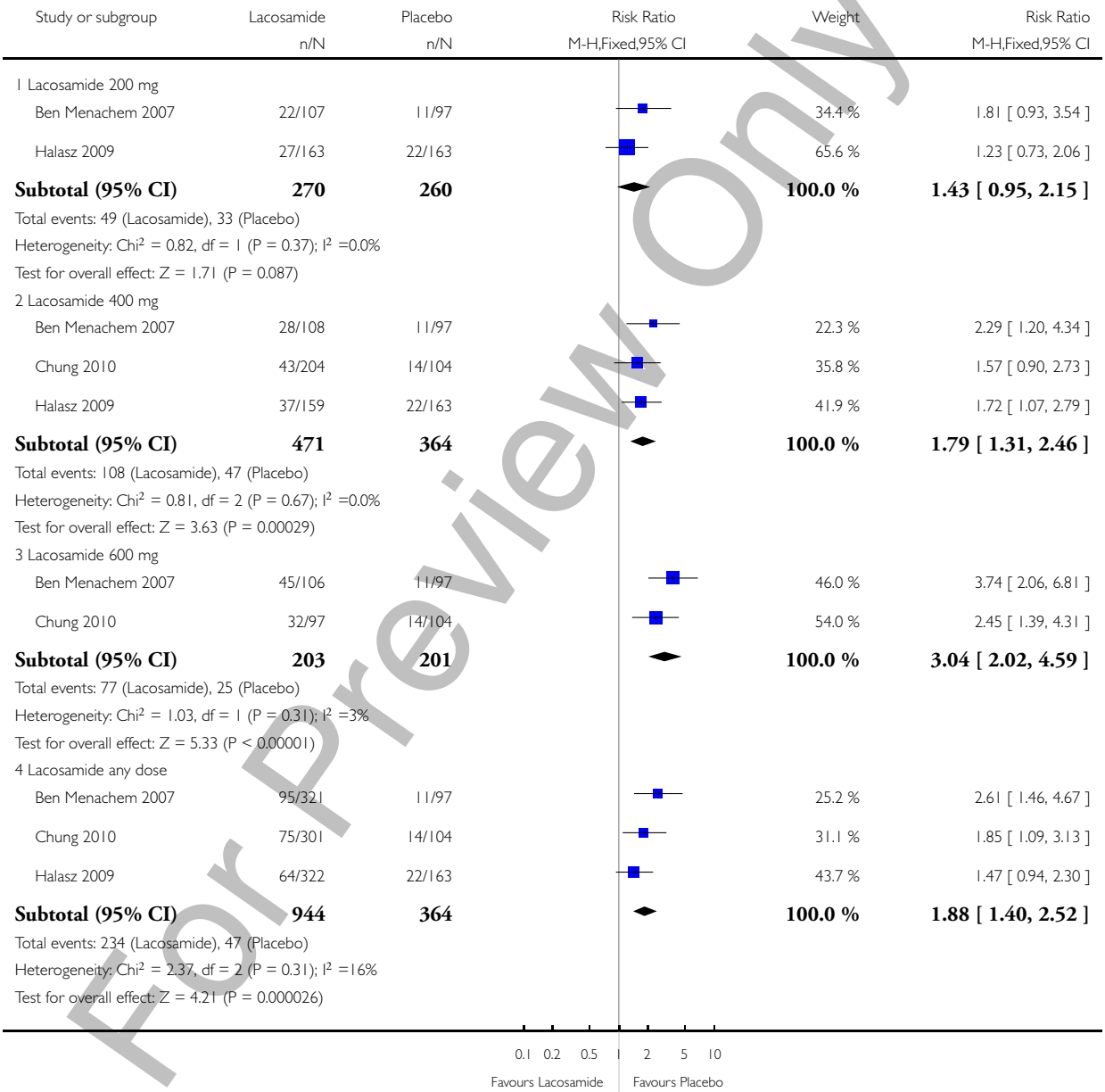


Analysis 1.3. Comparison 1 Lacosamide versus placebo, Outcome 3 Treatment Withdrawals.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 3 Treatment Withdrawals

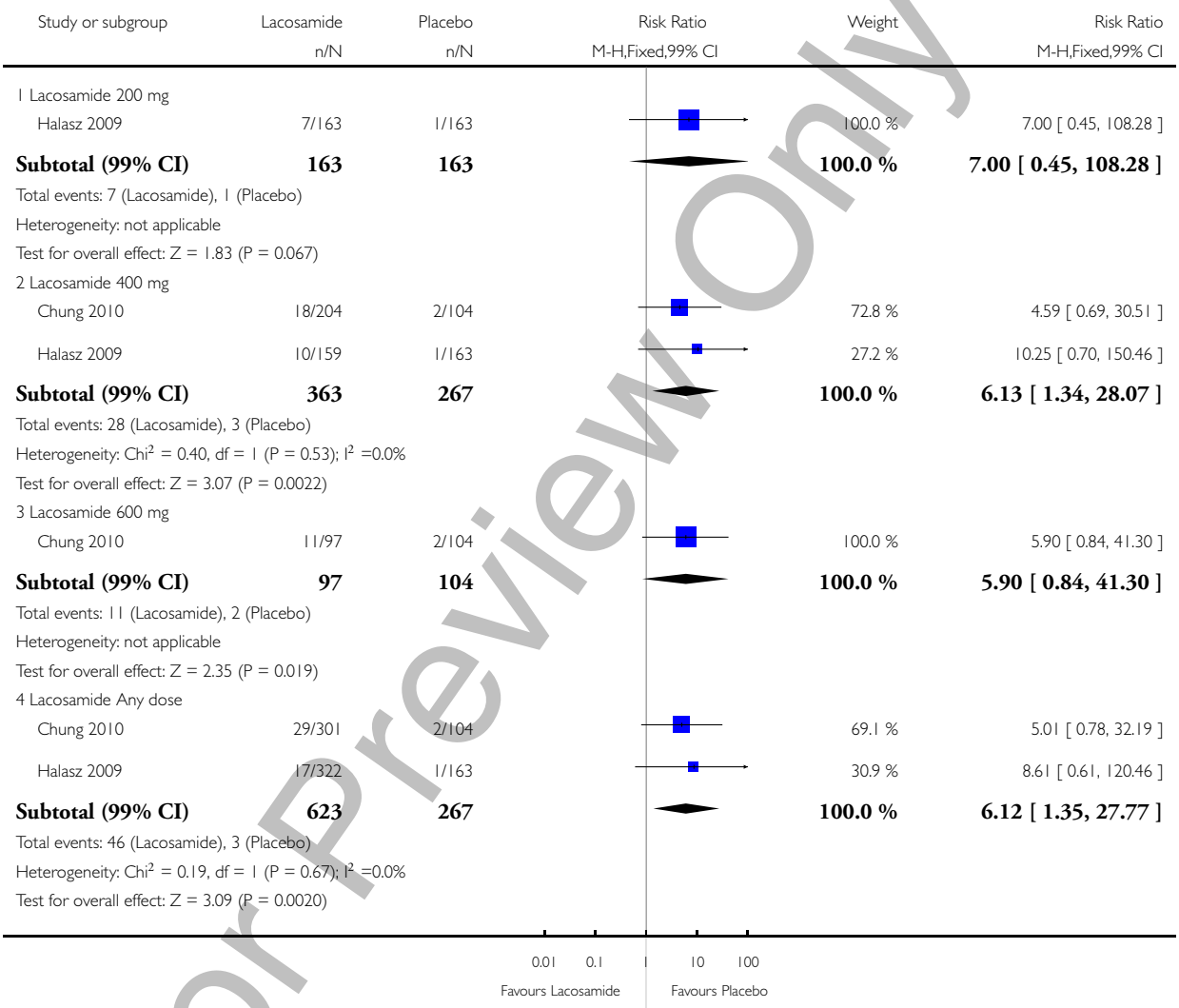


Analysis 1.4. Comparison 1 Lacosamide versus placebo, Outcome 4 Abnormal Coordination.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 4 Abnormal Coordination

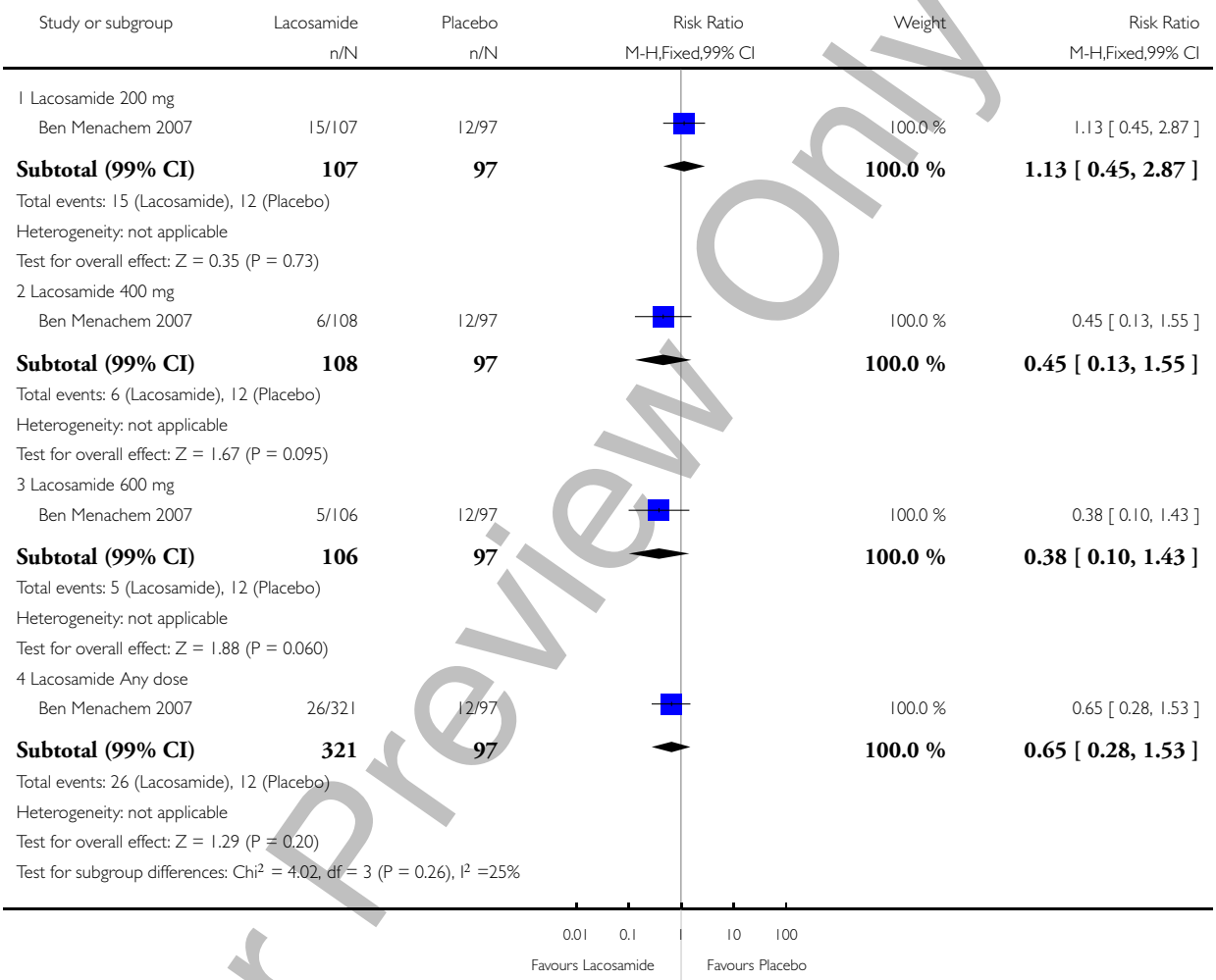


Analysis 1.5. Comparison 1 Lacosamide versus placebo, Outcome 5 Accident NOS.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 5 Accident NOS

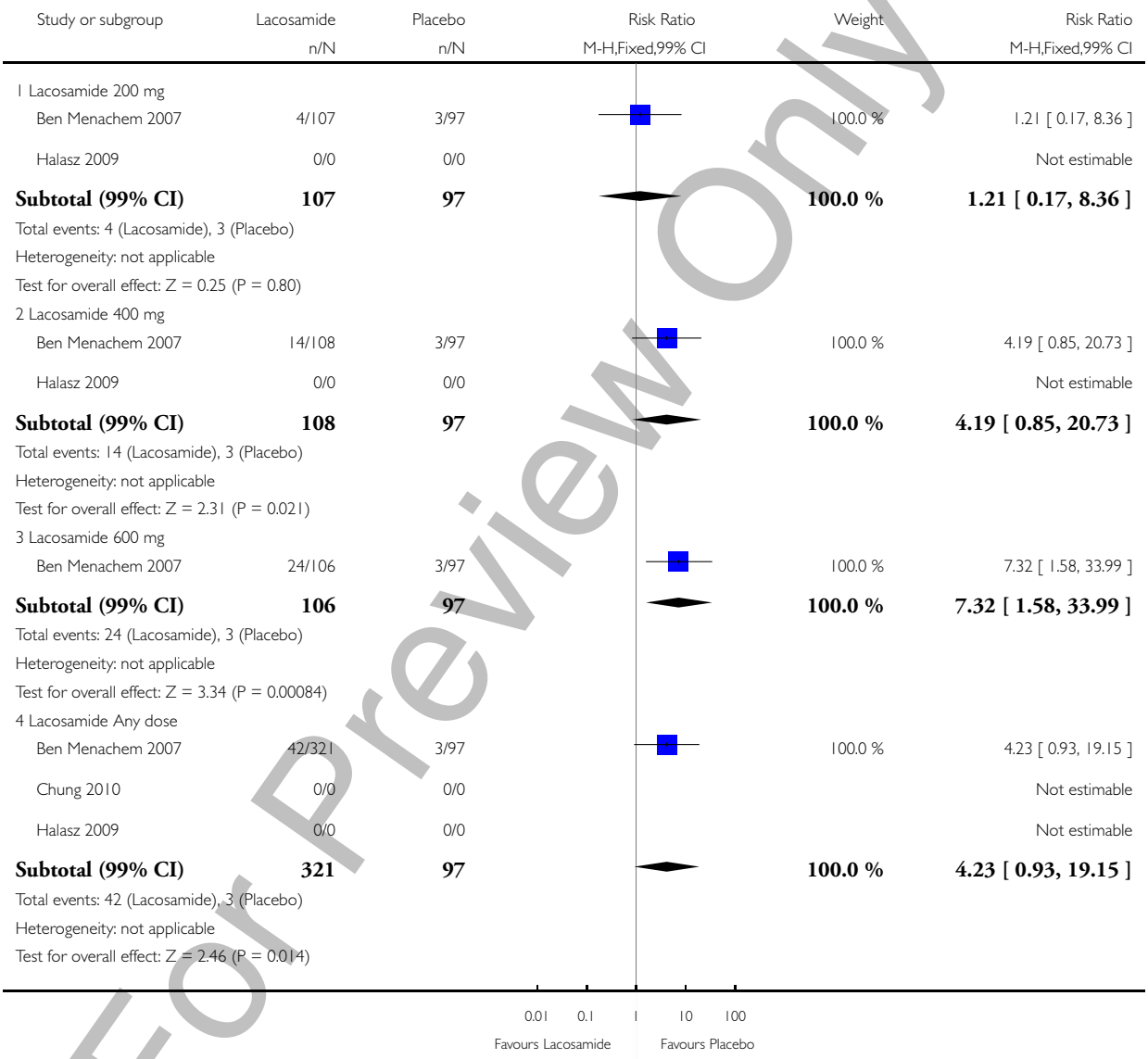


Analysis 1.6. Comparison 1 Lacosamide versus placebo, Outcome 6 Ataxia.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 6 Ataxia

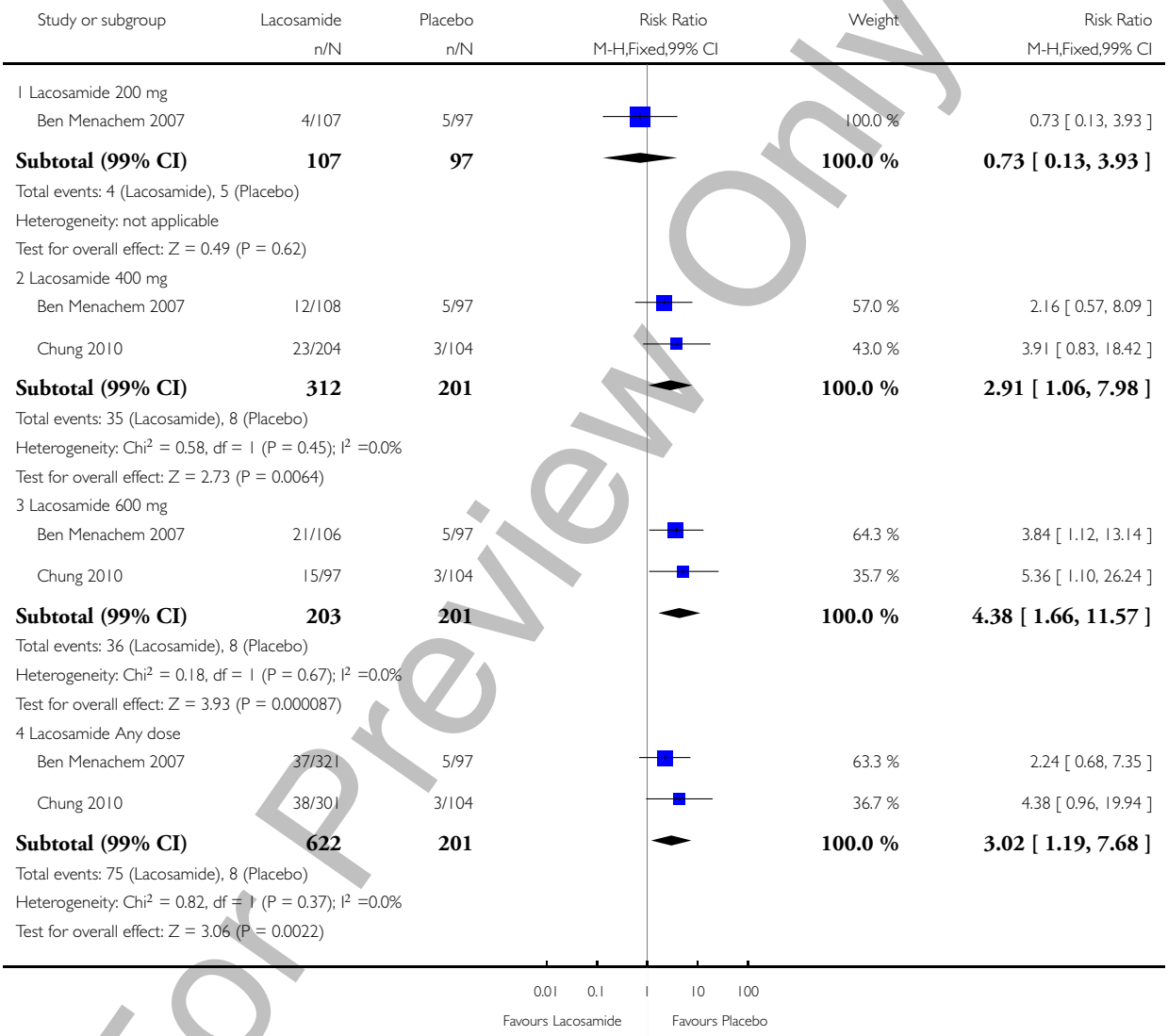


Analysis 1.7. Comparison 1 Lacosamide versus placebo, Outcome 7 Blurred Vision.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 7 Blurred Vision

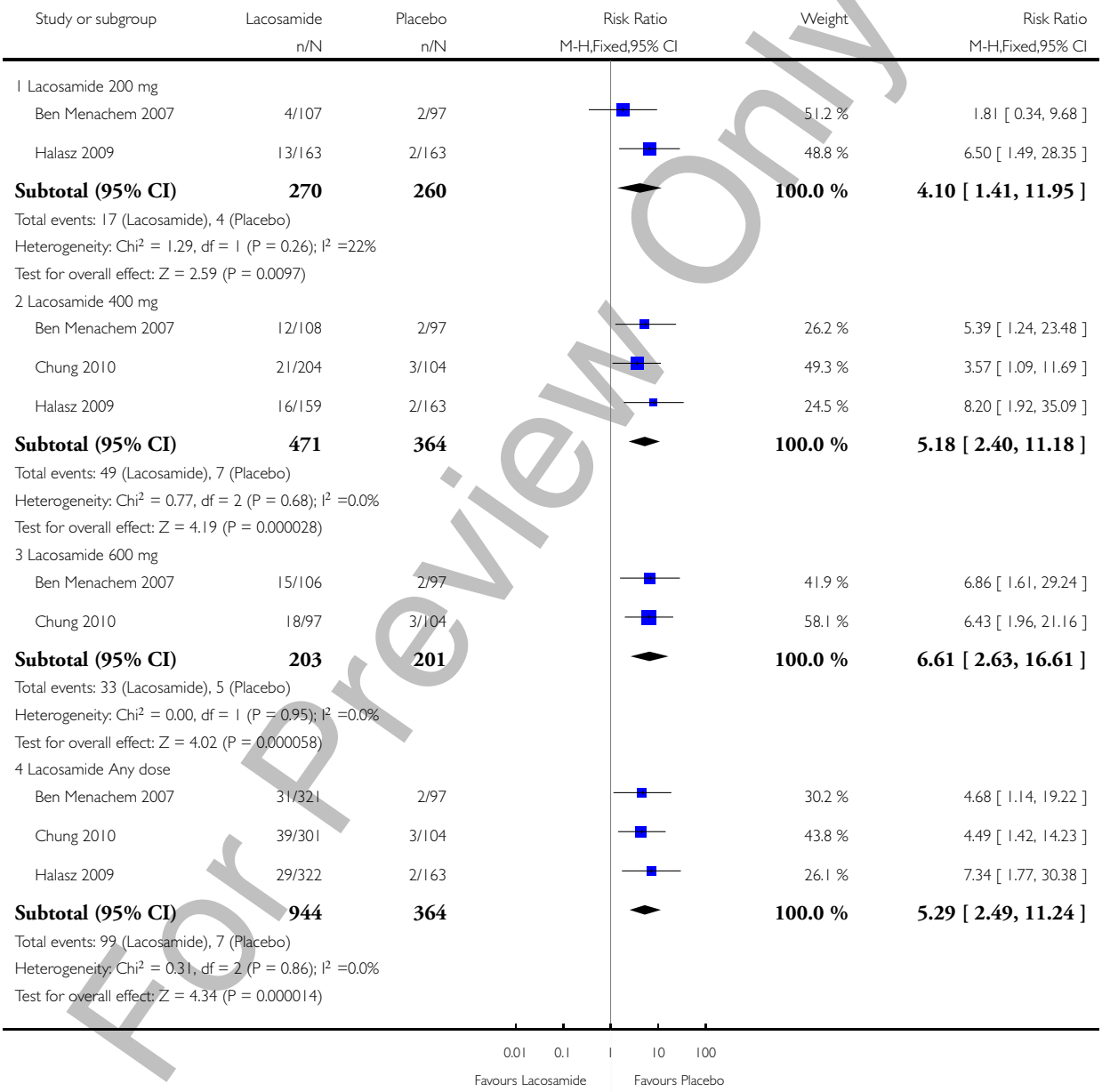


Analysis 1.8. Comparison 1 Lacosamide versus placebo, Outcome 8 Diplopia.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 8 Diplopia

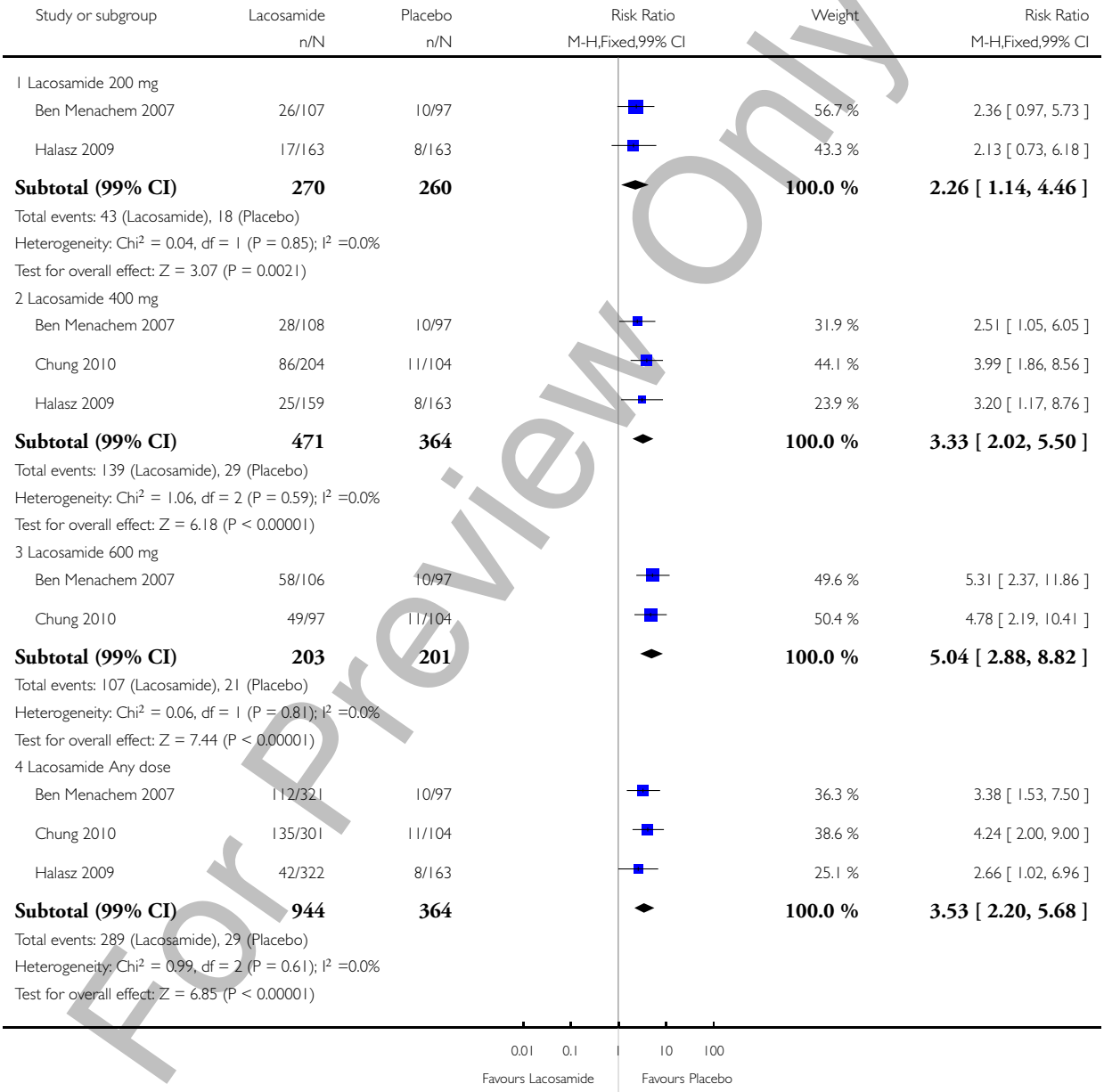


Analysis 1.9. Comparison 1 Lacosamide versus placebo, Outcome 9 Dizziness.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 9 Dizziness

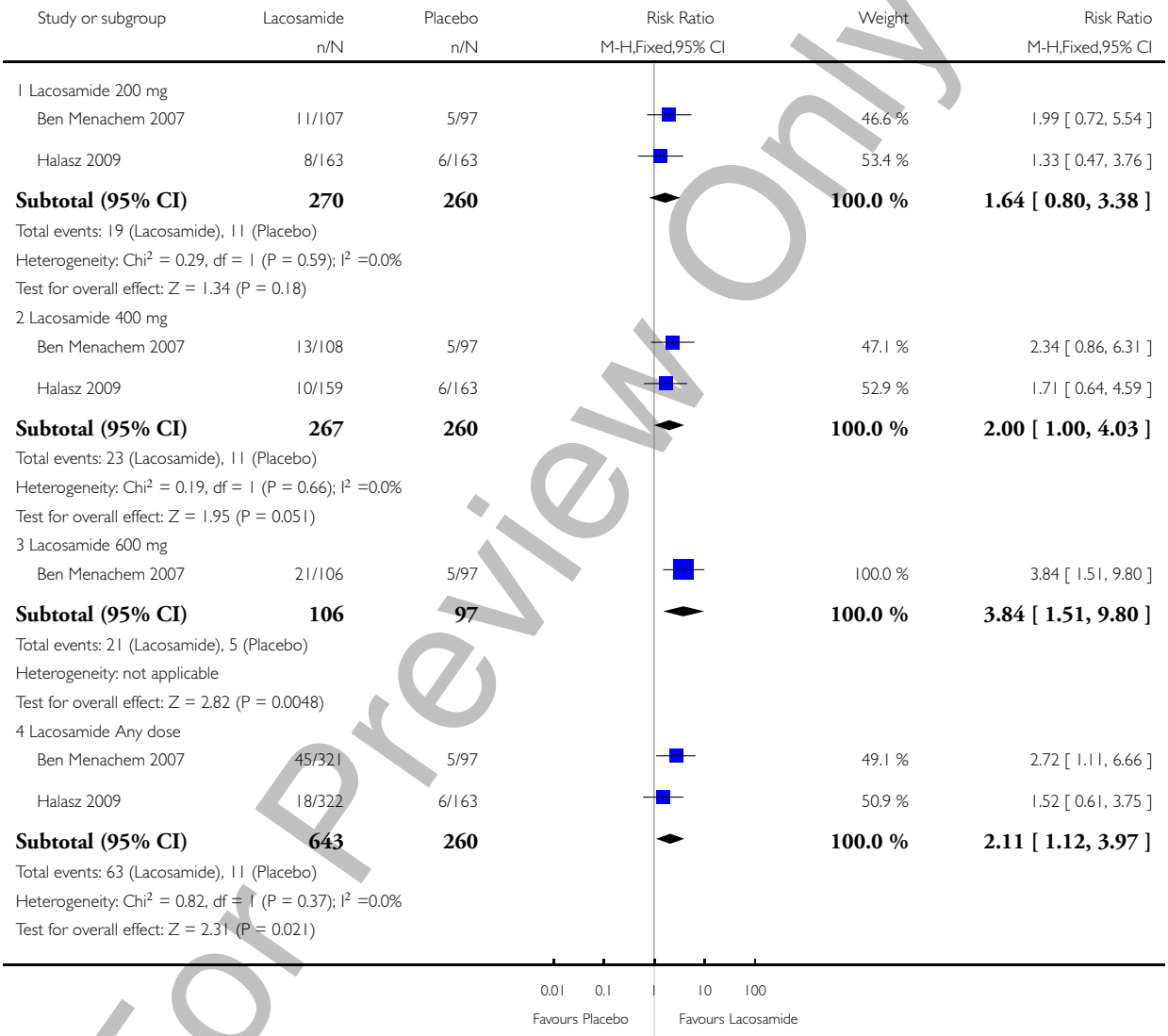


Analysis 1.10. Comparison 1 Lacosamide versus placebo, Outcome 10 Fatigue.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 10 Fatigue

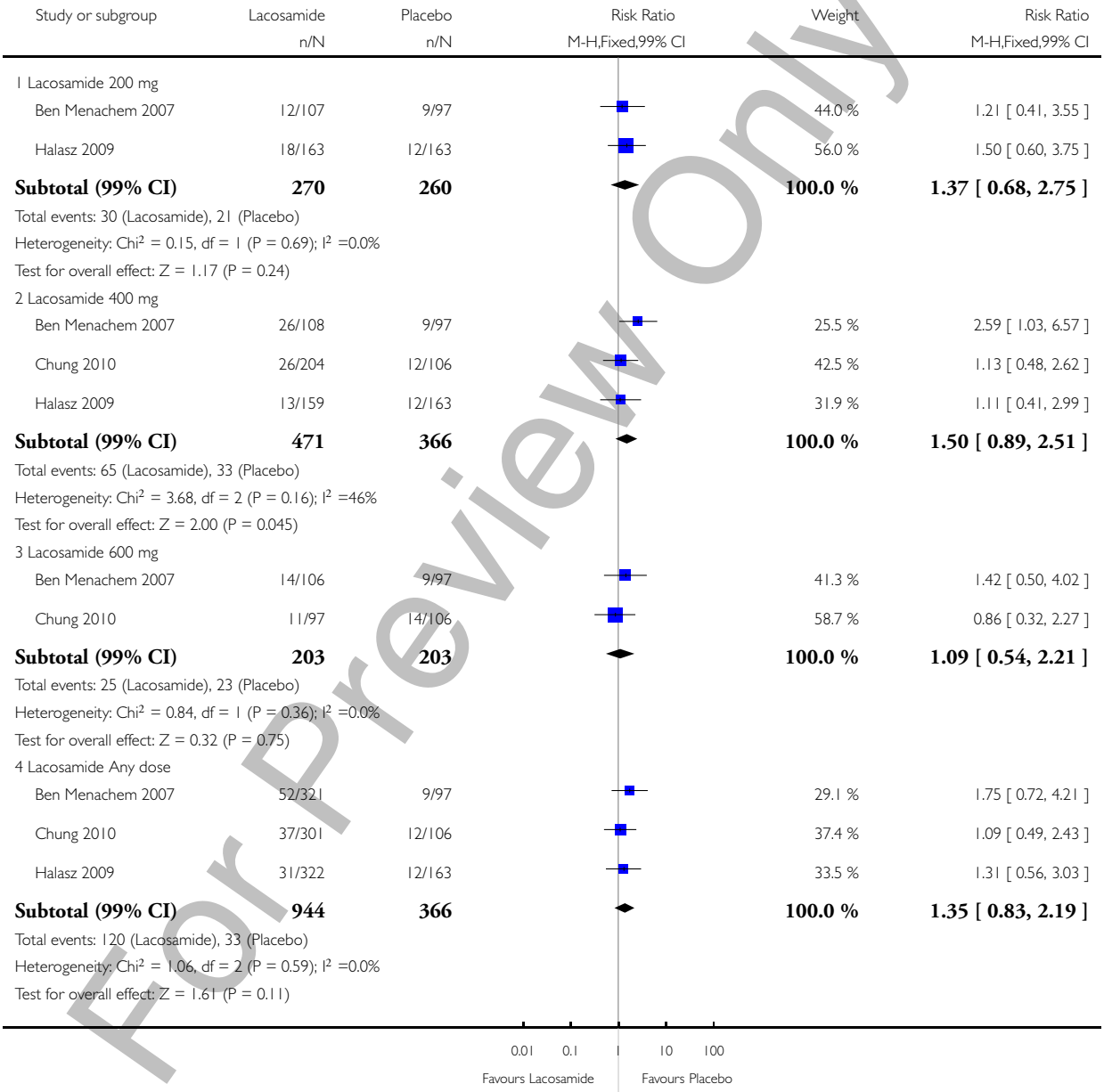


Analysis 1.11. Comparison 1 Lacosamide versus placebo, Outcome 11 Headache.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 11 Headache

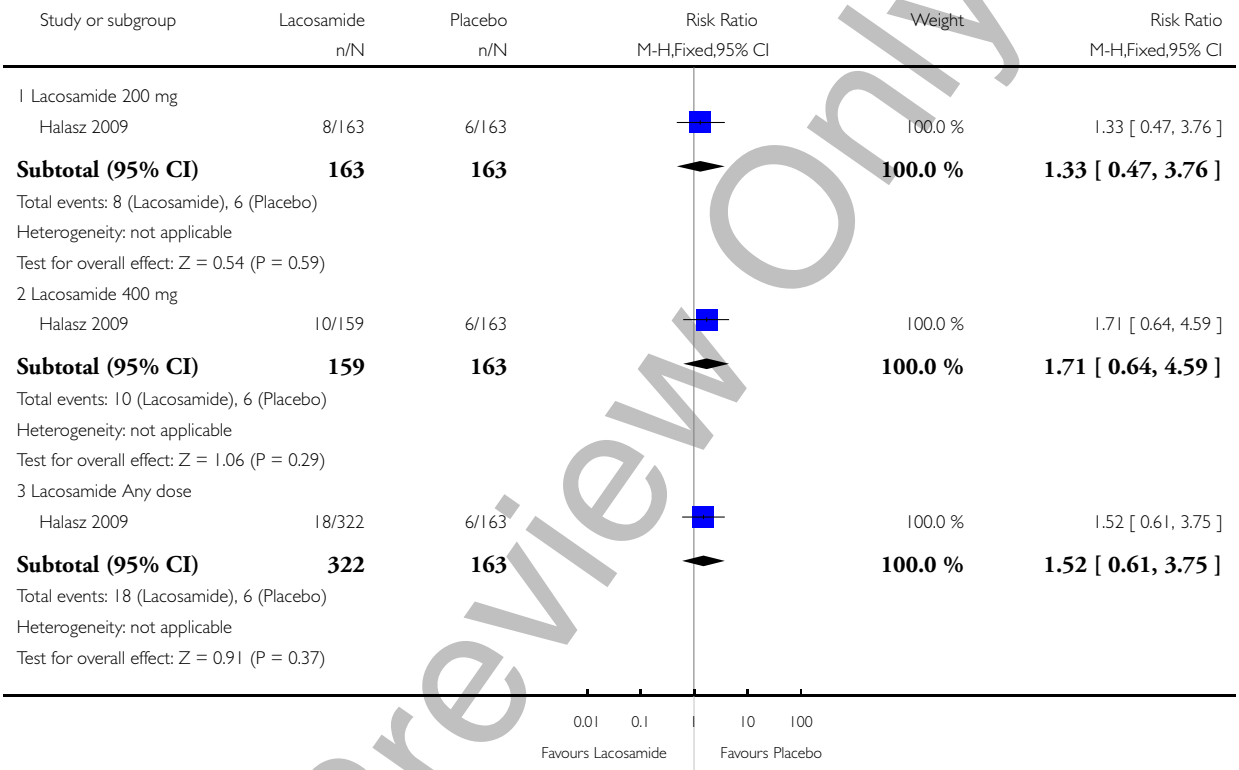


Analysis 1.12. Comparison 1 Lacosamide versus placebo, Outcome 12 Proportion of patients with Nasopharyngitis.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 12 Proportion of patients with Nasopharyngitis

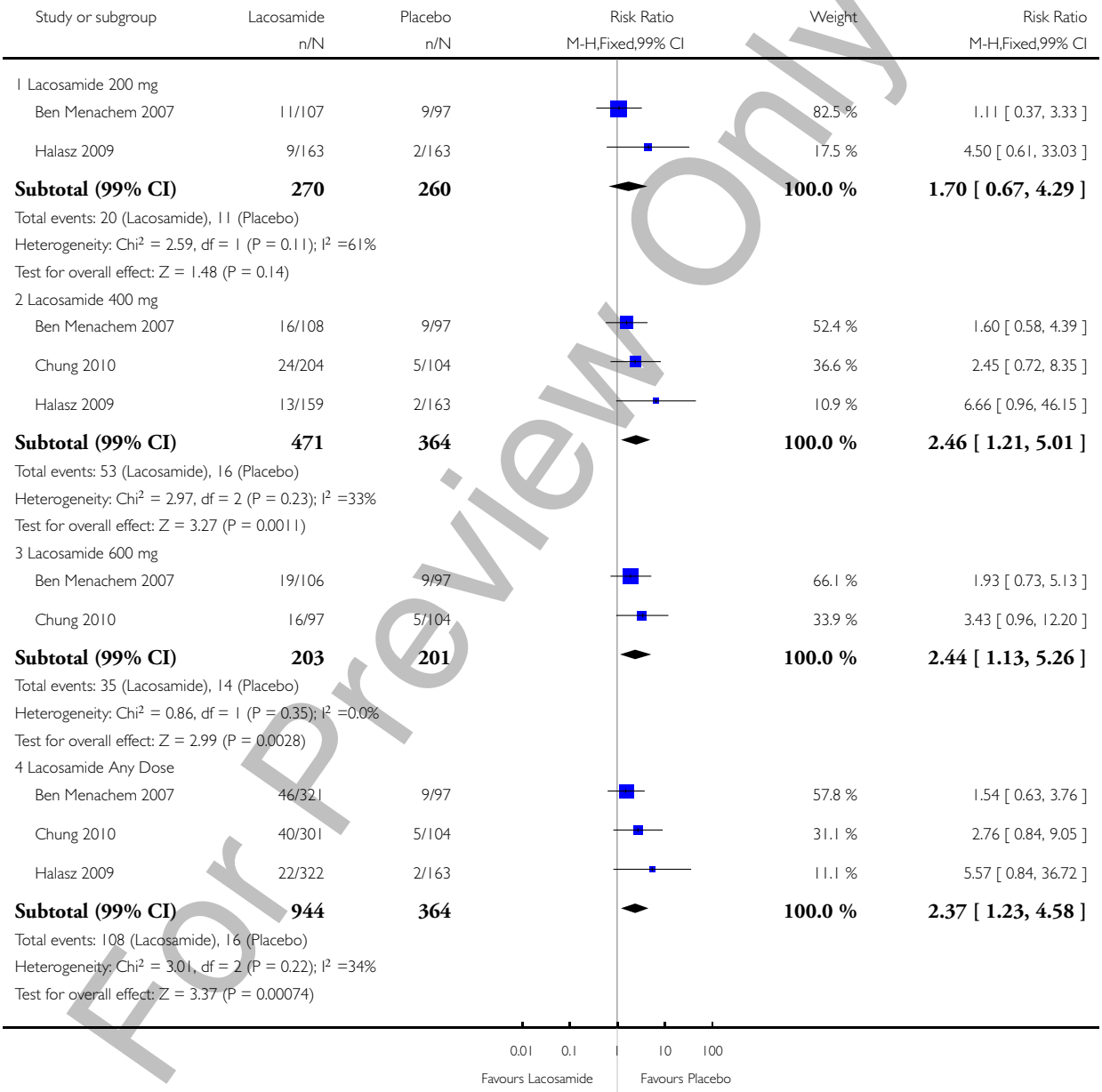


Analysis 1.13. Comparison 1 Lacosamide versus placebo, Outcome 13 Nausea.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 13 Nausea

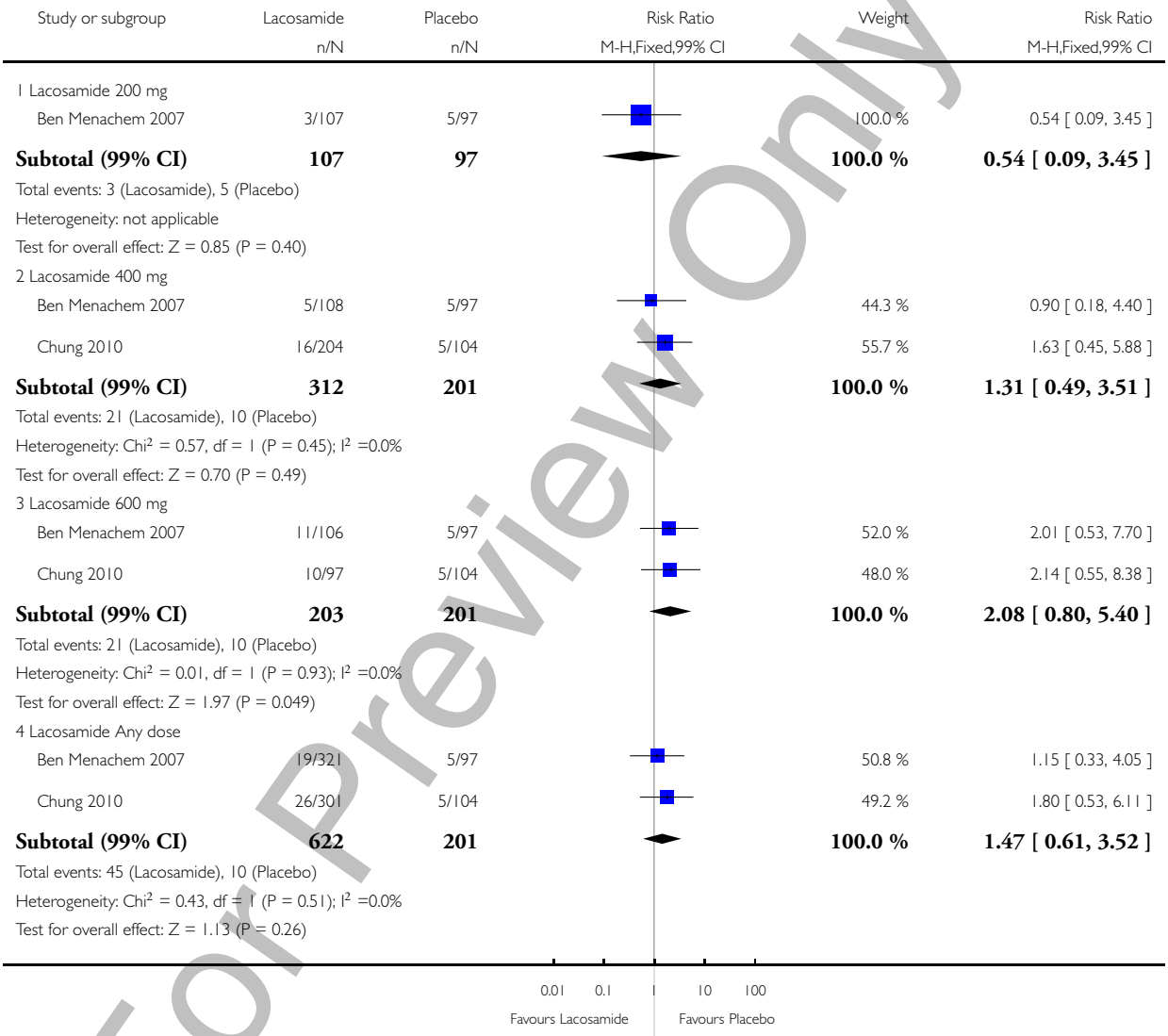


Analysis 1.14. Comparison 1 Lacosamide versus placebo, Outcome 14 Nystagmus.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 14 Nystagmus

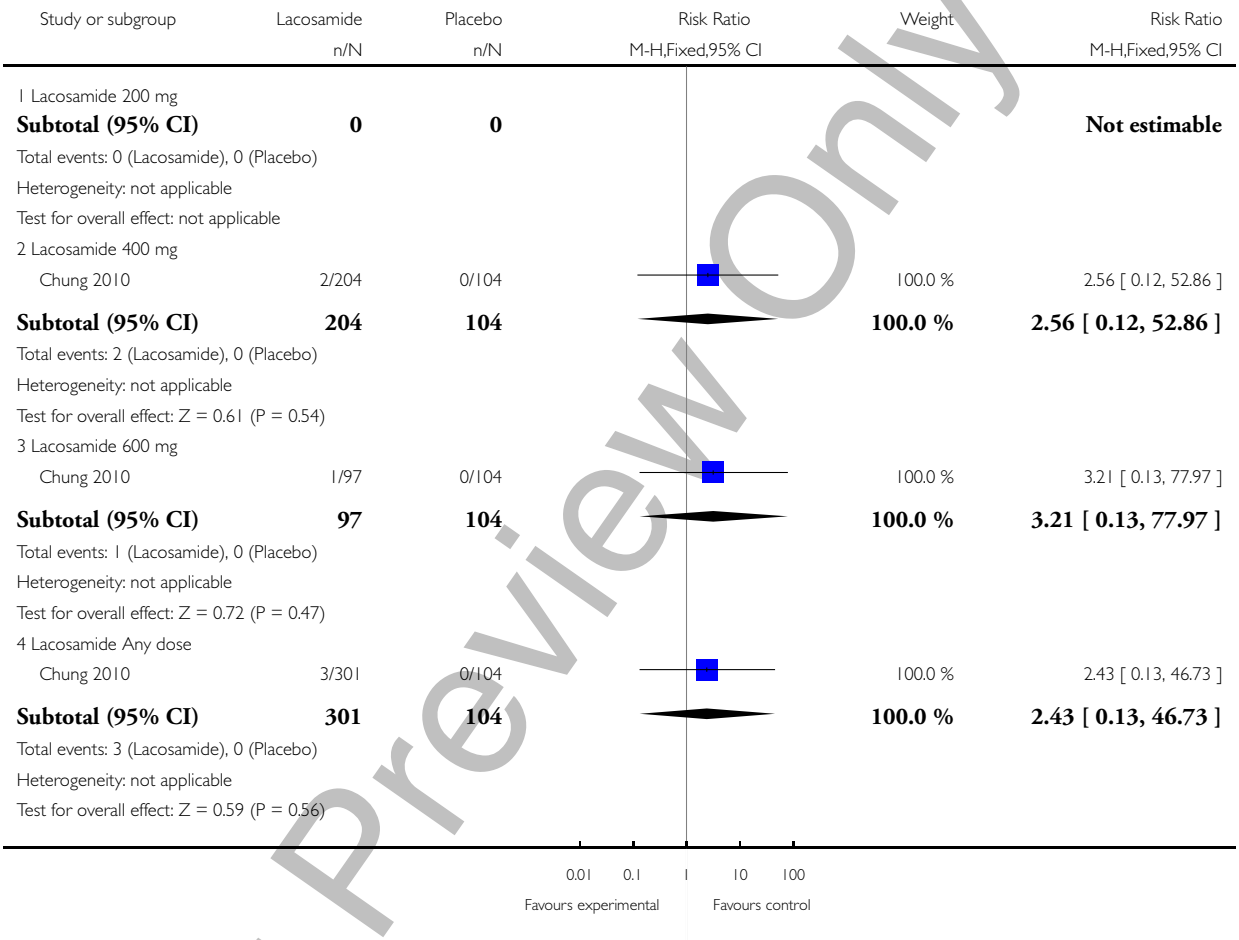


Analysis 1.15. Comparison 1 Lacosamide versus placebo, Outcome 15 Peripheral Edema.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 15 Peripheral Edema

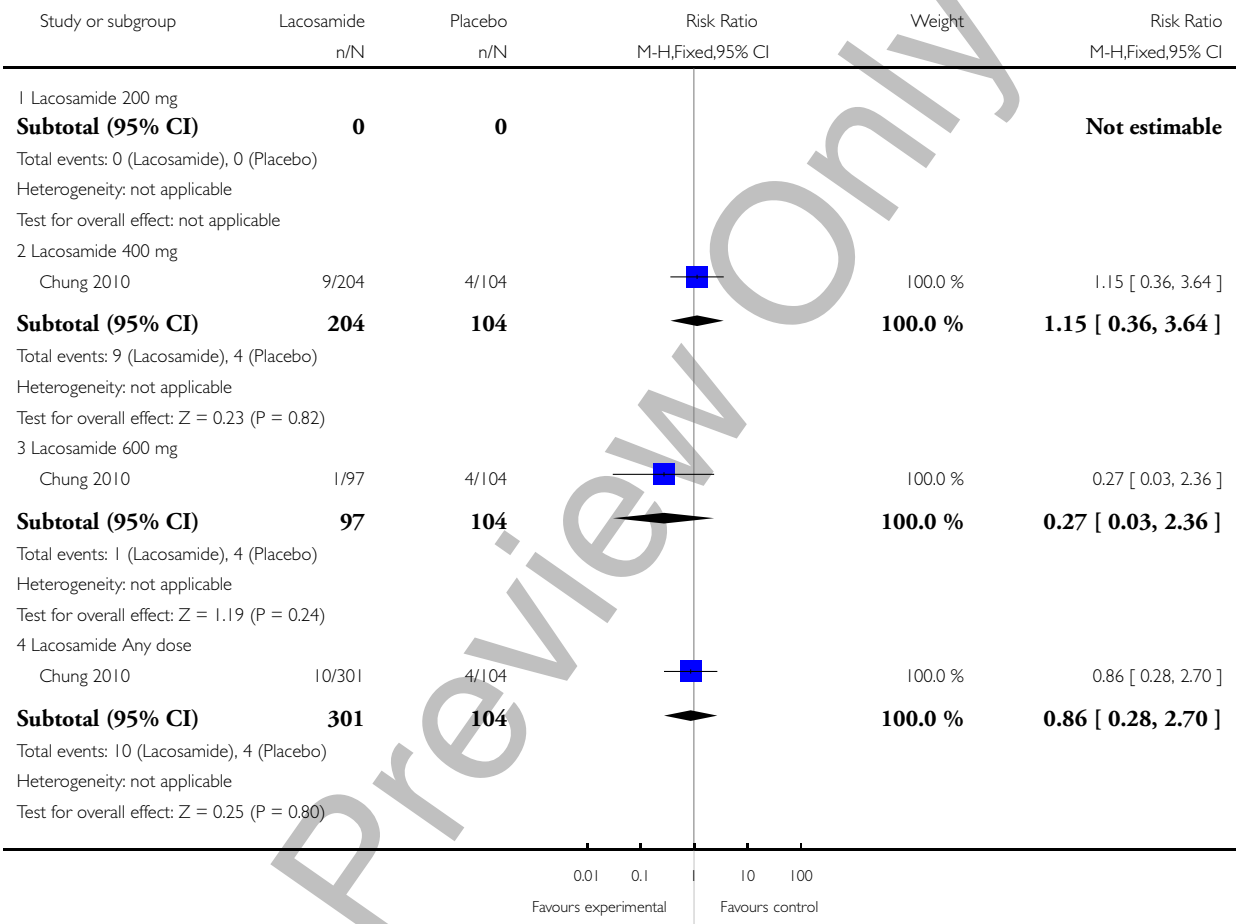


Analysis 1.16. Comparison 1 Lacosamide versus placebo, Outcome 16 Rash.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 16 Rash

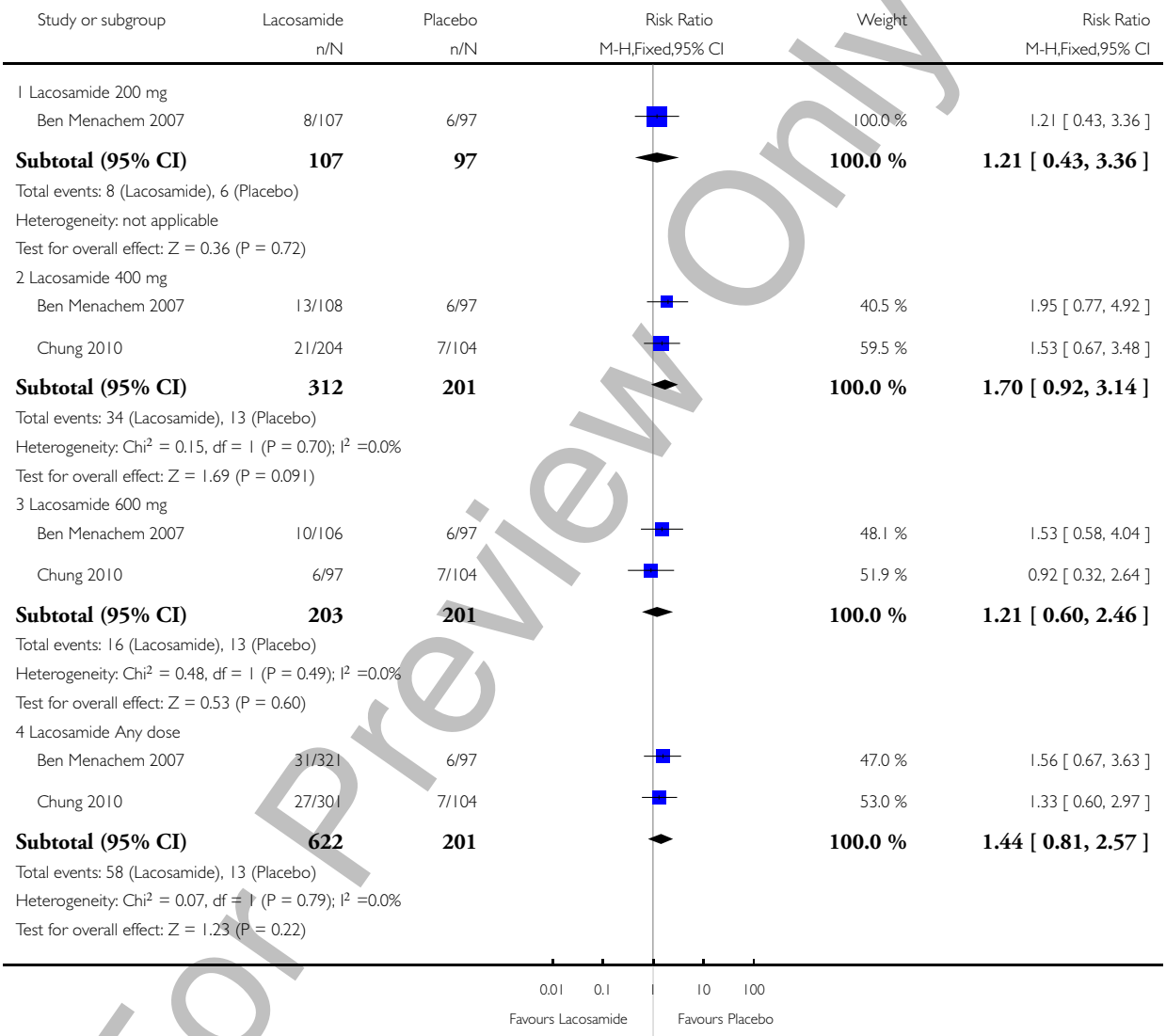


Analysis 1.17. Comparison 1 Lacosamide versus placebo, Outcome 17 Somnolence.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 17 Somnolence

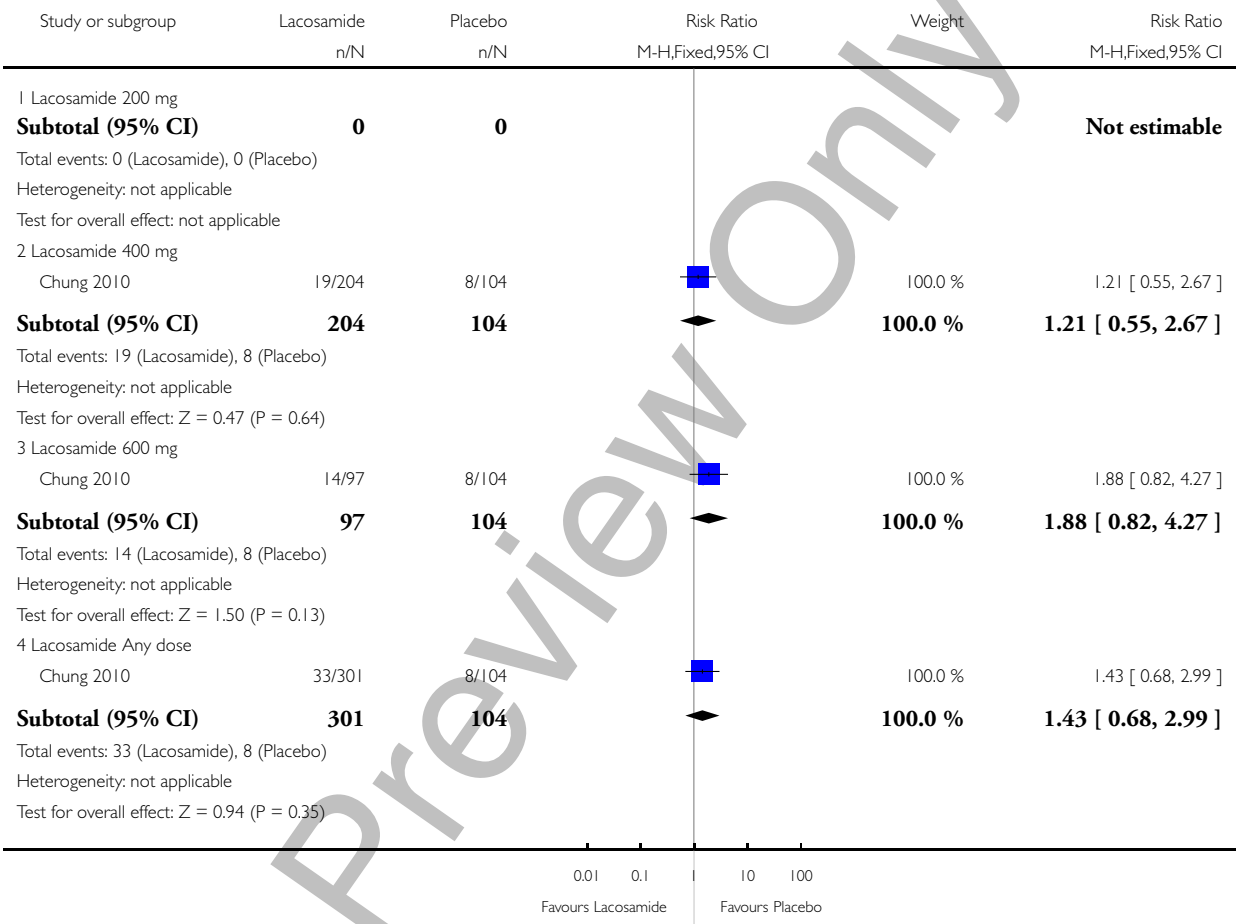


Analysis 1.18. Comparison 1 Lacosamide versus placebo, Outcome 18 Tremor.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 18 Tremor

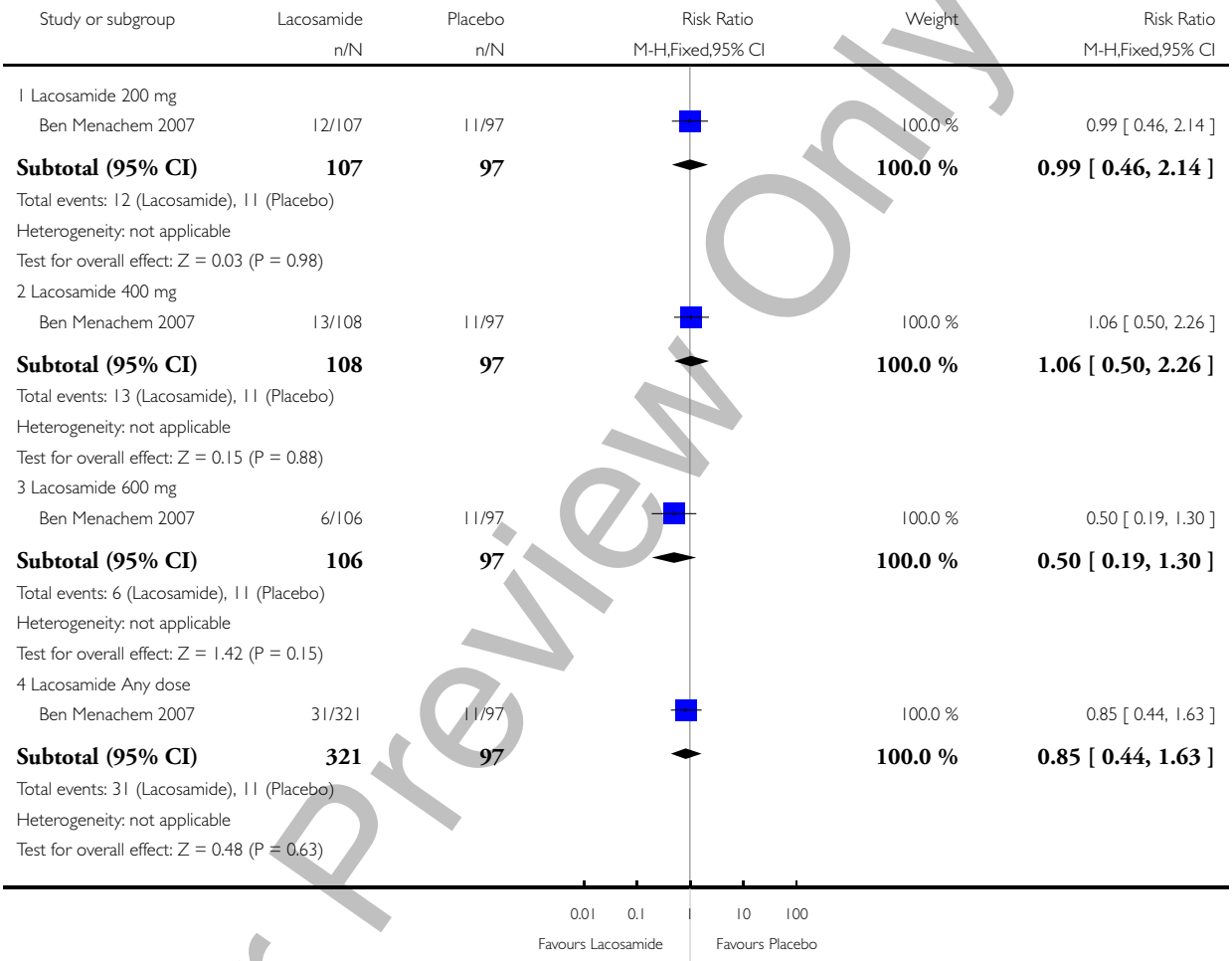


Analysis 1.19. Comparison 1 Lacosamide versus placebo, Outcome 19 Upper Respiratory Tract Infection.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 19 Upper Respiratory Tract Infection

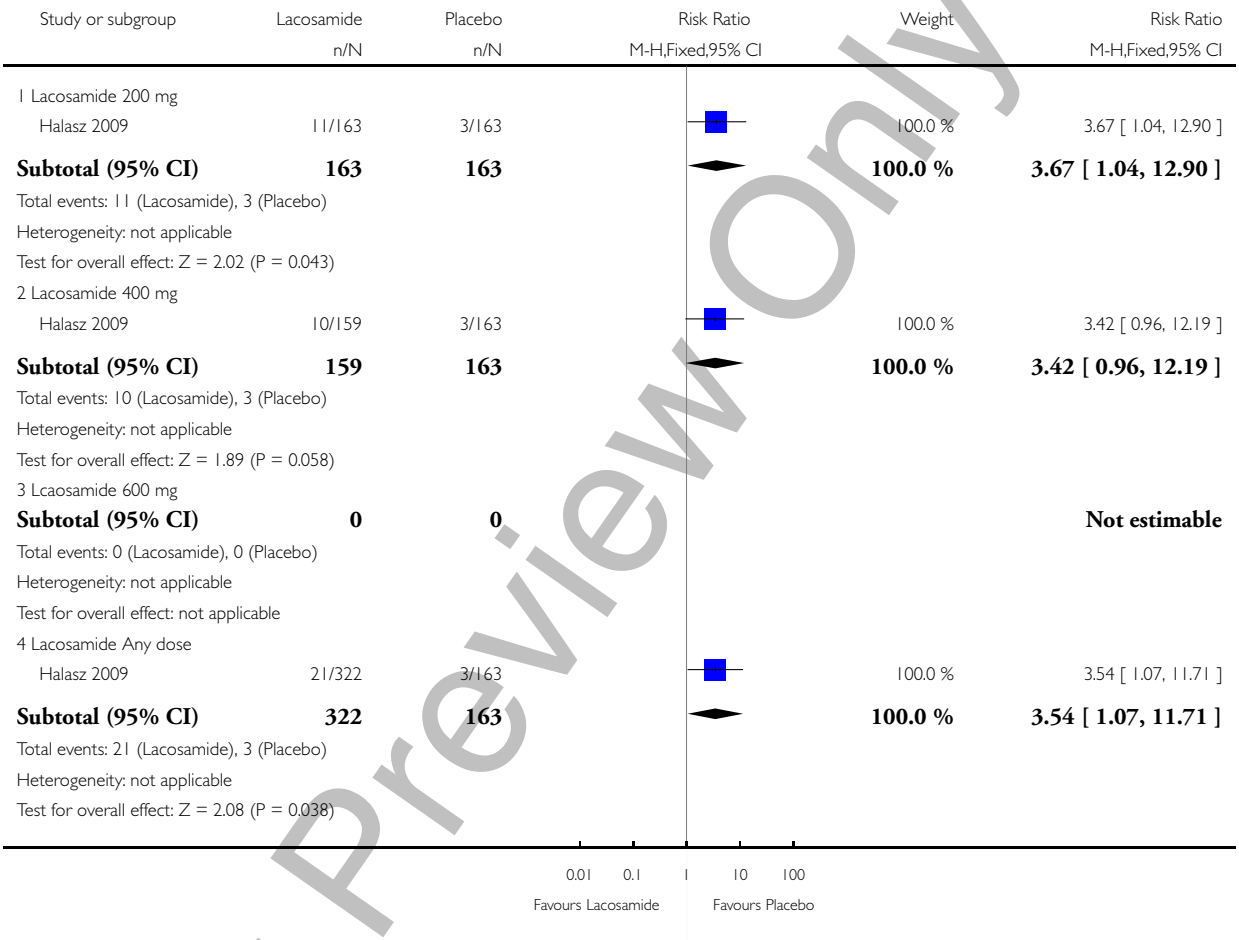


Analysis 1.20. Comparison 1 Lacosamide versus placebo, Outcome 20 Vertigo.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 20 Vertigo

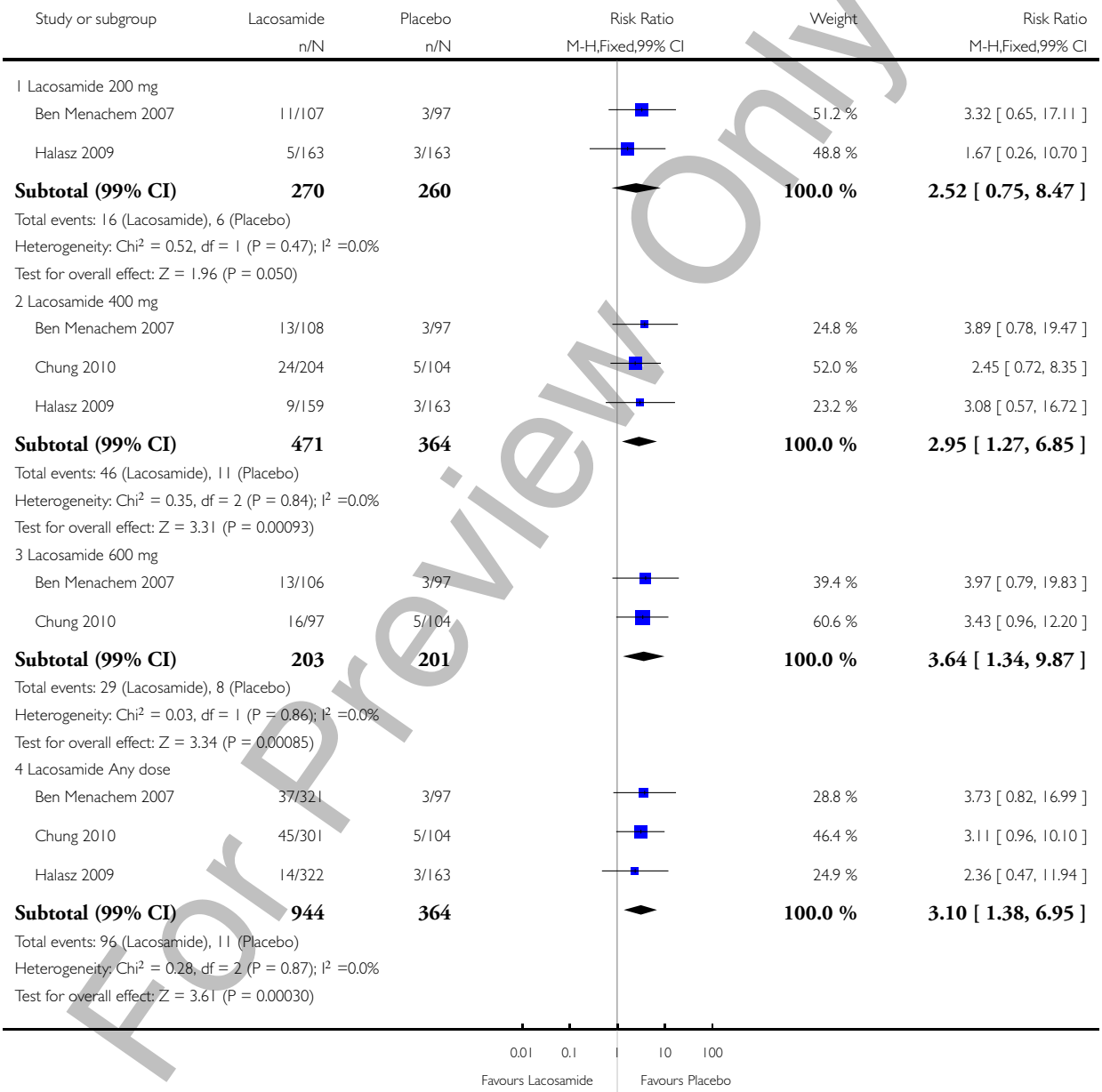


Analysis 1.21. Comparison 1 Lacosamide versus placebo, Outcome 21 Vomiting.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 21 Vomiting

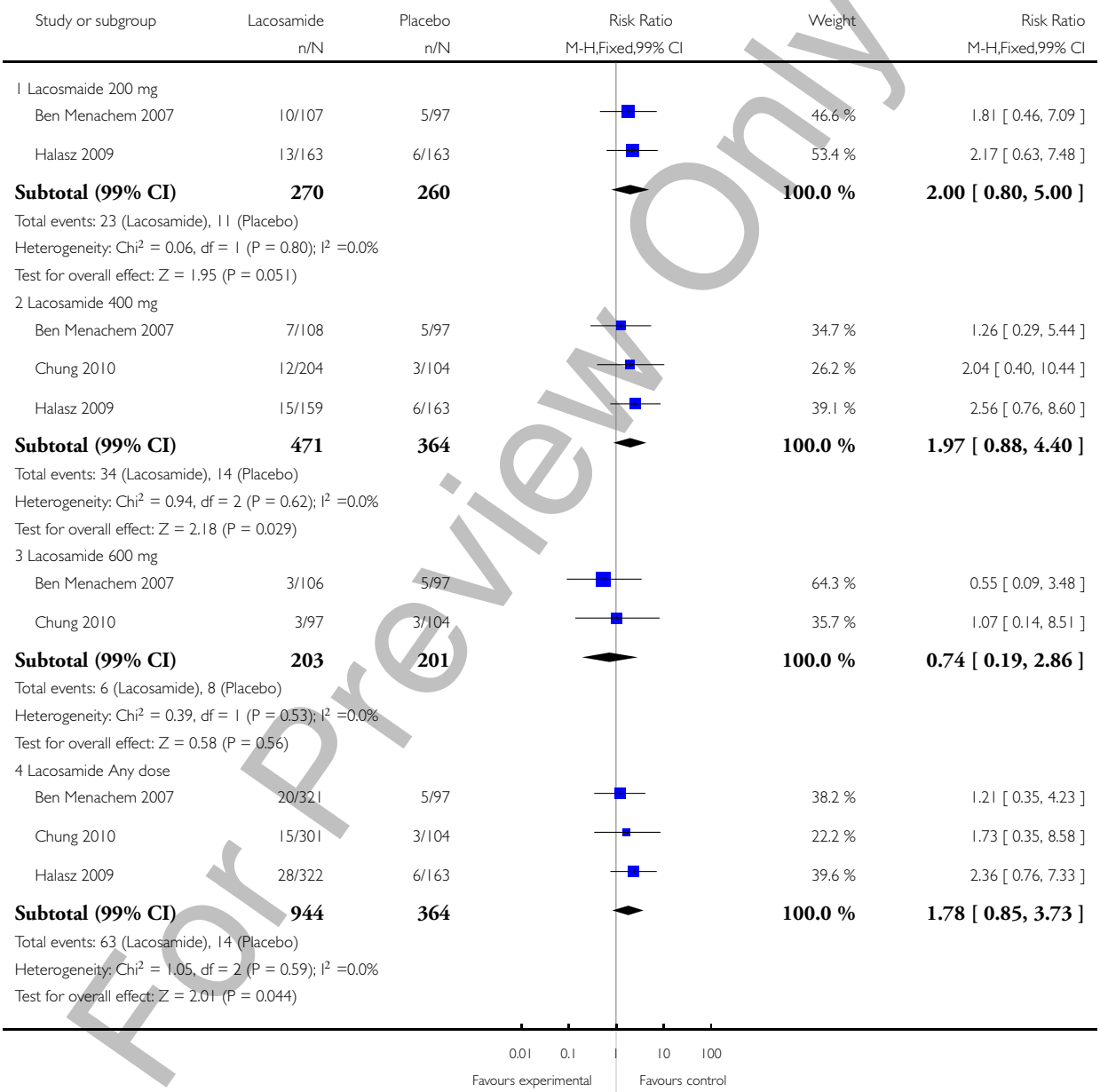


Analysis 1.22. Comparison 1 Lacosamide versus placebo, Outcome 22 Serious Adverse Events.

Review: Lacosamide add-on therapy for partial epilepsy

Comparison: 1 Lacosamide versus placebo

Outcome: 22 Serious Adverse Events



APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialised Register search strategy

#1 Lacosamide or Erlosamide or Harkoseride or Vimpat
#2 monotherap* not (adjunct* or "add-on" or "add on")
#3 (#1 NOT #2) AND INREGISTER

Appendix 2. CENTRAL search strategy

#1 Lacosamide or Erlosamide or Harkoseride or Vimpat
#2 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)
#3 MeSH descriptor: [Epilepsy] explode all trees
#4 MeSH descriptor: [Seizures] explode all trees
#5 (#2 or #3 or #4)
#6 MeSH descriptor: [Eclampsia] explode all trees
#7 #5 not #6
#8 #1 and #7
#9 monotherap* not (adjunct* or "add-on" or "add on")
#10 #8 not #9 in Trials

Appendix 3. MEDLINE search strategy

1. (Lacosamide or Erlosamide or Harkoseride or Vimpat).mp.
2. exp Epilepsy/
3. exp Seizures/
4. (epilep$ or seizure$ or convuls$).tw.
5. 2 or 3 or 4
6. exp Pre-Eclampsia/ or exp Eclampsia/
7. 5 not 6
8. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
9. clinical trials as topic.sh.
10. trial.ti.
11. 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. 1 and 7 and 13
15. (monotherap$ not (adjunct$ or "add-on" or "add on")).tw.
16. 14 not 15

Appendix 4. SCOPUS search strategy

((TITLE-ABS-KEY(lacosamide OR erlosamide OR harkoseride OR vimpat)) AND NOT (TITLE(monotherap* AND NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)))

CONTRIBUTIONS OF AUTHORS

Jennifer Pulman, Arif Shukralla and Andrew McKay collected data, conducted the analysis and compiled the text of the review. Prof Marson compiled the text of the review and assisted in the statistical analysis.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

The review presents independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Adverse Event reporting in Randomised Controlled Trials

A Systematic Review of Anti Epileptic Drugs using the CONSORT guidelines 2004

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Dept of Neuroscience* & Statistics§ University of Liverpool, United Kingdom

Introduction

➢Randomised Controlled Trials(RCTs) form the corner stone of evidence based medicine[1]

➢Treatment decisions require both an assessment of benefits and harms. One source of adverse event data is randomised controlled trials

➢The CONSORT group established in 1993 is a collaboration of scientists, clinicians , journal editors and members of the Cochrane Collaboration[2].

➢They provide clinicians and journal editors a comprehensive checklist of minimum requirements for adequate reporting of RCTs.

➢This list was revised in 2004 to incorporate adverse events and reporting of harms.

➢The CONSORT guidelines for RTCs can be used as a quality measurement tool.

Aim

➢To review the reporting of adverse events in RCTs of antiepileptic drugs.

➢To assess both qualitatively and quantitatively the current standards of Adverse Event reporting.

➢To address any deficiencies.

➢To provide recommendations for improvement

Methods

SEARCH CRITERIA

- We used MEDLINE and The Cochrane Library for RCTs dated between 1999 and 2008.
- Key words used: ‘Epilepsy’ ‘Anti epileptic Drugs’ and ‘Seizures’
- Limits imposed: English language, Phase 1, 2, 3 and 4.

ELIGIBILTY CRITERIA

- RCT assessing an antiepileptic drug.
- Minimum of two comparison groups including placebo.

EXCLUSION CRITERIA

- Surgical or Vagus nerve interventions.
- Clinical trials with a neuropsychological test as primary outcome.

DATA COLLECTION

- We collected data on, trial design, funding, year of publication, journal of publication and patient demographics.
- We analyzed data using the 10 recommendations published by CONSORT.

ANALYSIS

➢Each of the ten CONSORT recommendations had a number of sub items.

➢This totalled the number of sub items to 20 per RCT as shown in fig 1 and 2.

➢Each RCT was compared with the CONSORT guidelines to determine if each guideline was met as seen in figure 5 and 6.

Item	CONSORT	Section in article	Description
1	1	Title & abstract	Title and abstract must state of adverse events if study collected data.
2	2	Introduction	Intention to address adverse events
3	3	Methods	All or treatment emergent adverse events
4	3	Methods	Validated instrument used to collect adverse events
5	3	Methods	Validated dictionary of adverse events used
6	4	Methods	How adverse events are collected
7	4	Methods	Is the timing of collection of adverse events stated
8	4	Methods	Indicate details of attribution of adverse events
9	5	Methods	Describe plans for any statistical analysis

***Figure one**: Consort criteria one to five*

Item	CONSORT	Section in article	Description
10	6	Results	Report early or late withdrawals due to AE
11	6	Results	Report Serious adverse events including deaths
12	6	Results	Provide tabular description of AE
13	7	Results	Provide denominators for analysis on harms
14	8	Results	Presented separately for each group
15	8	Results	Provide the severity or grade of events
16	8	Results	Provides both the number of adverse events and the number of patients with adverse events
17	9	Results	Provide any subgroup analysis for AE
18	10	Discussion	Prior literature with reference to AE discussed
19	10	Discussion	Gives a balanced discussion of harms vs. efficacy
20	10	Discussion	Limitations of study with regard to adverse event data is presented

***Figure two**: Consort criteria six to ten*

➢Inter-rater reliability was assessed by comparing completed forms for 10% of the total sample.

➢Two reviewers randomly selected studies and compared collected data.

Results

1. A total of 2050 abstracts between January 1999 and Dec 2008 were reviewed.
2. Only 150 trials met the inclusion criteria and were reviewed in full
3. Mean inter-rater reliability for 15 trials analyzed was 90 percent.

		Number of Trials n= 150
Demographics	Adults	77
	Children	29
	Adults and Children	44
Epilepsy type	Focal	101
	Generalised	7
	Both Focal and General	42
Therapy	Add on	85
	Monotherapy	65
Funding	Industry	94
	Non Industry	56
Scope	Efficacy and Safety	137
	Efficacy only	9
	Safety only	4
Centre	Multi centre	124
	Single Centre	26
Median duration in wks	28 weeks	

***Figure Three**: Summary of collected papers*

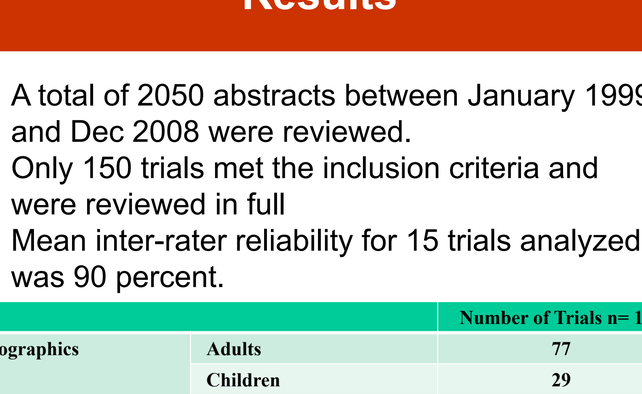

***Figure four**: Proportion of trials reporting Adverse event data as number of patients, percentage of patients and number of adverse events*

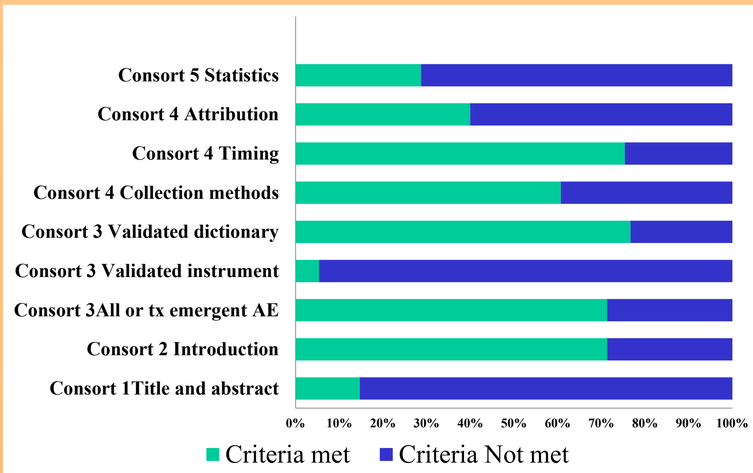

***Figure five:** Percentage of trials meeting each individual CONSORT criteria (Criteria 1 to 5 shown)*

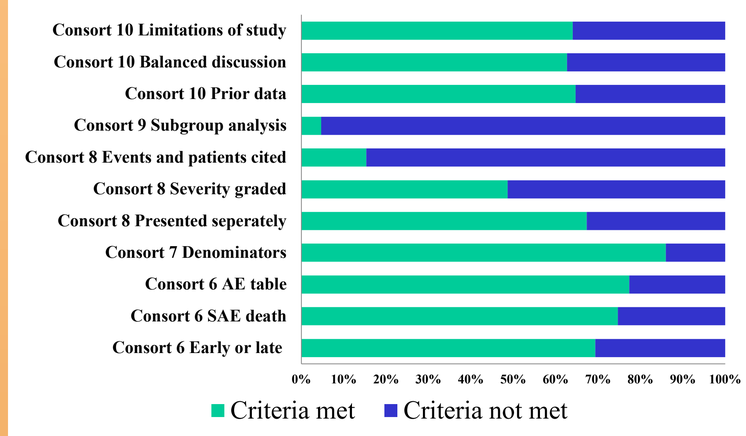

***Figure six:** Percentage of trials meeting each individual CONSORT criteria (Criteria 6 to 10 shown)*

➢Adverse event reporting in the methodology section is poor.

➢Very few trials provide details of attribution of adverse events or use a validated tool for the collection of adverse events as shown in figure 5.

➢Adverse events are better reported in the results section but fewer trials report both the number of events and patients as illustrated in figure 4 and 6.

Conclusion

➢Majority of trials report the results of adverse events in accordance to the CONSORT criteria. RCTs report results better than methods of AE collection.

➢RCTs meet minimum requirements for reporting it but the quality of the data is still poor due to limited reporting of statistical analysis, details of attribution and lack of valid tools for adverse event collection.

➢If only trials that meet the minimum standards are allowed to formulate systematic reviews then this automatically introduces bias. Current reporting of adverse events may result in bias in systematic reviews and limit the assessment of benefit and harm.

References

1 John M. Lachin, John P. Matts and L.J. Wei: **Randomization in clinical trails: Conclusions and recommendations** *Controlled Clinical trails 1998 Vol 9 Issue 4 pg 365-375*

2 John P.A Ioannidis et al: **Better reporting o Harms in Randomized Trials: An Extension of the CONSORT statement** *Annals of Internal Medicine 2004 Vol 141 pg 781-788*

Funding: supported by a Grant from NIHR research council United Kingdom
No conflict of interest declared

Reporting of Adverse Events in Randomised Controlled Trials

A review of antiepileptic drugs

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Dept of Molecular and Clinical Pharmacology[1] & Dept of Biostatistics[2]

UNIVERSITY OF LIVERPOOL

INTRODUCTION

- Randomised controlled trials (RCTs) form the cornerstone of evidence based medicine.
- Treatment decisions require an assessment of harms and benefits.
- Efficacy outcomes are reported well in RCTs but few studies have evaluated adverse event (AE) reporting.
- Guidelines for reporting harms were published by the CONSORT group in 2004[1].
- These could be used as a quality assessment tool for assessing current deficiencies.

AIMS

- To asses the reporting of adverse events in RCTs of antiepileptic drugs.
- To highlight current inadequacies of reporting adverse events.
- To provide recommendations for improvements in reporting.

METHODS

Inclusion Criteria:

- We searched for reports of RCTs published between 1999 and 2008 using MEDLINE and the Cochrane Library database.
- Reports of antiepileptic drugs were included.
- RCTs should have a minimum of two comparator groups, one of which could be placebo.

Exclusion Criteria:

- Observational studies.
- Surgical interventions or vagus nerve stimulation studies.
- Neuropsychological outcomes as the primary outcomes or secondary reports of RCTs where this is the key outcome.

Analysis:

- We selected 23 items relating to harms from the CONSORT guidelines.
- We scored trial reports using the guidelines. Scores could range from a minimum of zero to 23.
- We compared proportions of trials meeting individual items. Subgroups used were: Industry funded versus non Industry funded, trials recruiting children versus adults, trials published before and after the publication of the CONSORT guidelines.
- Cohen's Kappa statistic was used to determine inter-rater agreement.
- We used unpaired *t* test to compare score totals and we calculated relative risks for meeting individual criteria.

Item	CONSORT	Section in article	Description
1	1	Title or abstract	Title or abstract must state if adverse events outcomes were analysed
2	2	Introduction	Intention to address adverse events
3	3	Methods	Definitions of adverse events
4	3	Methods	All or selected sample of adverse events
5	3	Methods	Treatment emergent adverse events
6	3	Methods	Validated instrument used to collect adverse events
7	3	Methods	Validated dictionary of adverse events used
8	4	Methods	How adverse events are collected
9	4	Methods	Is the timing of collection of adverse events stated
10	4	Methods	Indicate details of attribution of adverse events
11	5	Methods	Describe plans for any statistical analysis
12	5	Methods	Describe plans for handling recurrent events

***Figure one**: CONSORT criteria one to five*

Item	CONSORT	Section in article	Description
13	6	Results	Report early or late withdrawals due to AE
14	6	Results	Report serious adverse events including deaths
15	7	Results	Provide definitions used for analysis set
16	7	Results	If same analysis set used for efficacy and safety
17	7	Results	Provide denominators for analysis of harms
18	8	Results	Presented separately for each group
19	8	Results	Provide the severity or grade of events
20	8	Results	Provides both the number of adverse events and the number of patients with adverse events
21	10	Discussion	Prior literature with reference to AE discussed
22	10	Discussion	Gives a balanced discussion of harms vs. efficacy
23	10	Discussion	Limitations of study with regard to adverse event data is presented

***Figure two**: CONSORT criteria six to ten*

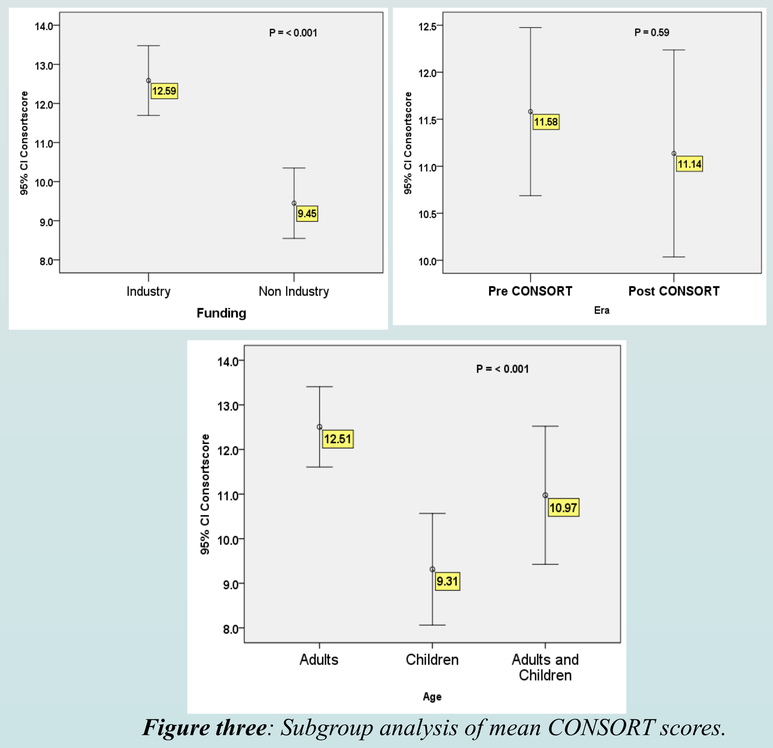
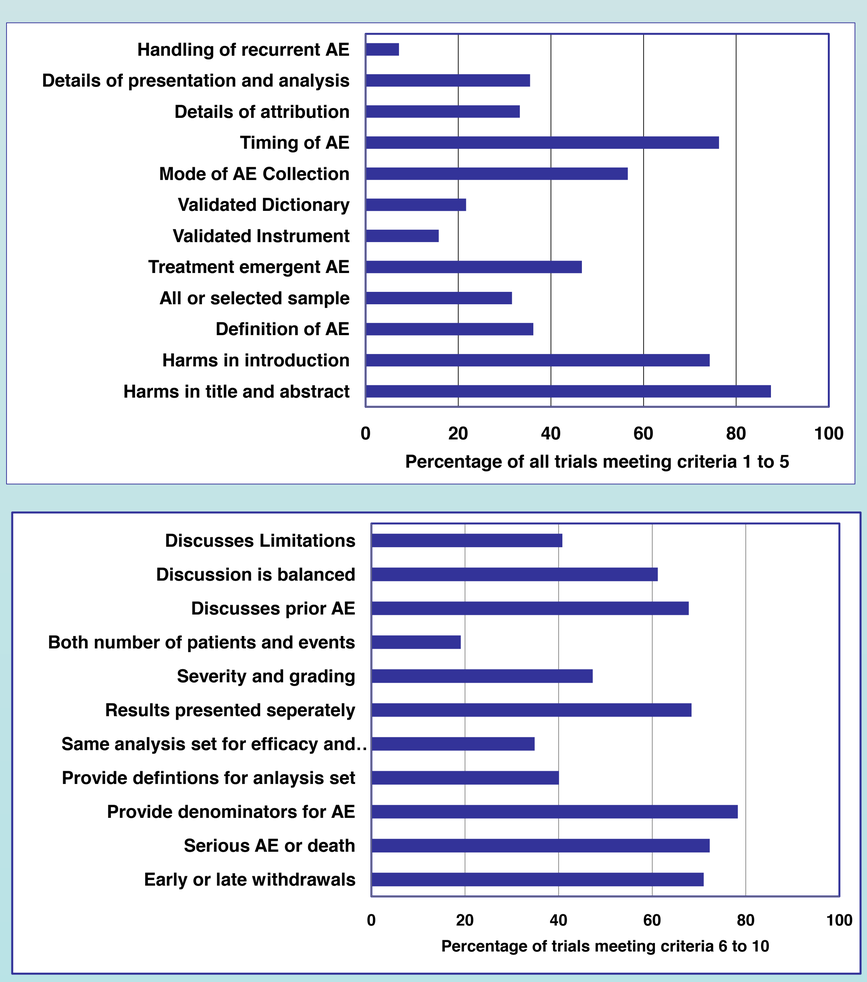
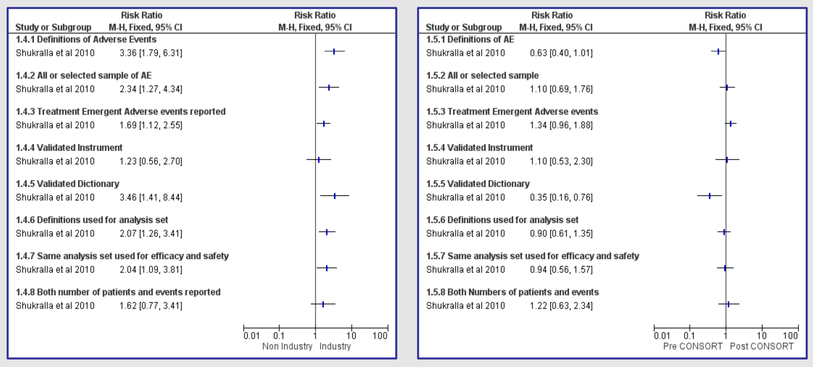


***Figure three**: Subgroup analysis of mean CONSORT scores.*





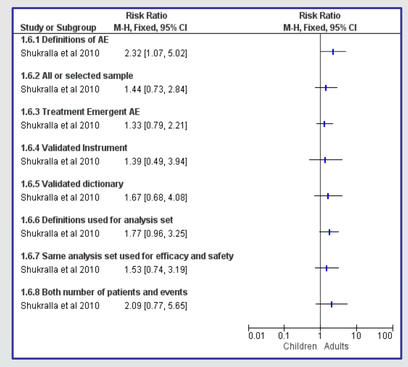


***Figure four**: Relative risks of meeting individual CONSORT items*

RESULTS

- Our search revealed 152 eligible trial reports
- Inter-rater agreement for scoring was deemed to be good. Cohen's kappa value of 0.78 (95% CI 0.64-0.92).

Industry funded trials.

- Scored better than non industry funded studies.
- Relative risks comparing industry funded and non industry funded trials showed industry funded trials significantly excelled at a number of items. Examples include: providing definitions for AE, if all or selected sample of AE was reported, and if a validated dictionary was used.

Post CONSORT trials.

- Scored no different to Pre CONSORT trials.
- Relative risks were heterogeneous in size effect and direction.

Adult vs. Children.

- Trials recruiting adults scored better than those recruiting children.
- Relative risks showed trials recruiting adults were better at proving definitions for AE, providing details of statistical analysis, reporting withdrawals from AE and presenting results separately.

CONCLUSION

1. Reporting of adverse events is poor in current literature.
2. Reporting of outcomes is heterogeneous with some reported well and others being under reported.
3. Reporting has not changed since the CONSORT guidelines were published.
4. Industry sponsored trials are better at reporting harms outcomes.
5. Poor reporting adversely affects future prospects of including harms data into systematic reviews.
6. Our results reinforce work highlighting poor reporting in RCTs of antiretroviral drugs[3].
7. We recommend that journal editors should make authors aware of the guidelines relating to harms as there is evidence that other aspects of trial reporting has improved since publication of the original guidelines[2].

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3. Reporting of adverse events in randomised controlled trials of highly active antiretroviral therapy. Chowers M . Gottesman B Journal of Antimicrobial Chemotherapy. Vol 64 Pg 239-250.

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Adverse events of antiepileptic drugs across indications.

Can randomised controlled trial data from non-epilepsy indications be included in meta-analysis for AEDs used in epilepsy?

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INTRODUCTION

- Randomised controlled trials (RCTs) form the cornerstone of evidence based medicine.
- Treatment decisions require an assessment of harms and benefits.
- Meta-analysis is one method of summarizing efficacy and harms data from several RCTs.
- AEDs which are used in epilepsy are also used in other conditions like neuropathy and headache syndromes.
- Using harms outcomes from other indications in meta-analyses of AEDs provides additional data thus increases statistical power of the analysis.

AIMS

- To asses if harms data from indications other than epilepsy be used in meta-analyses of AEDs.
- To determine if heterogeneity between patients from trials in other indications is significant.
- To determine the sources of heterogeneity using meta-regression[2].

METHODS

Inclusion Criteria:

- We searched for reports of placebo controlled RCTs of AEDs in MEDLINE and the Cochrane Library database.
- RCTs recruited patients with either epilepsy, peripheral or CNS pain, and headache syndromes.
- Only AEDs of adults patents were included.
- AEDs included were: Topiramate, gabapentin, lacosamide, oxycarbazepine, valproate, carisbamate, pregabalin and zonisamide.

Exclusion Criteria:

- Observational studies.
- Surgical interventions or vagus nerve stimulation studies.
- Neuropsychological outcomes as the primary outcomes or secondary reports of RCTs where this is the key outcome.

Analysis:

- We selected 6 adverse events outcomes: dizziness, ataxia, headache, fatigue, somnolence nausea and proportion of patients with any AE and proportion of patients withdrawing due to AEs.
- We used RevMan 5.0 to calculate relative risks comparing placebo and active treatment.
- We sub grouped outcomes by indication to calculate I^2 test of statistical heterogeneity[1].

Meta-regression:

- To investigate on further sources of heterogeneity we eliminated the effect of dose using meta-regression.
- Intercept of regression curve would allow calculation of relative risks for each subgroup.

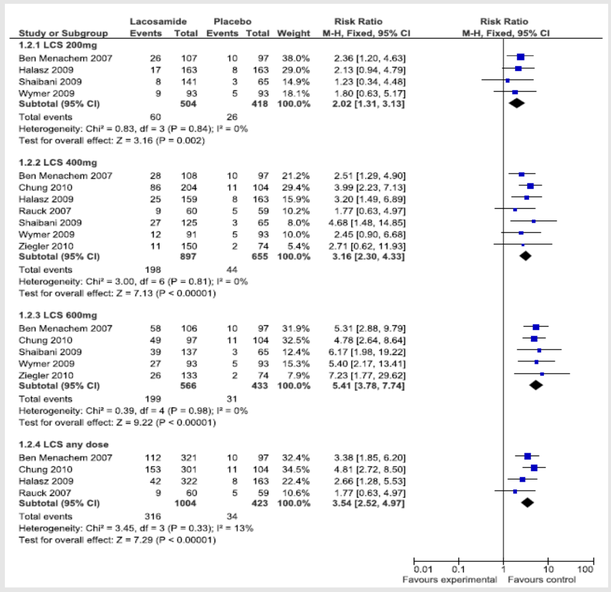


Fig 1. Forest plot of relative risk of dizziness by Lacosamide, sub grouped by dose . Data showing epilepsy and neuropathy trials

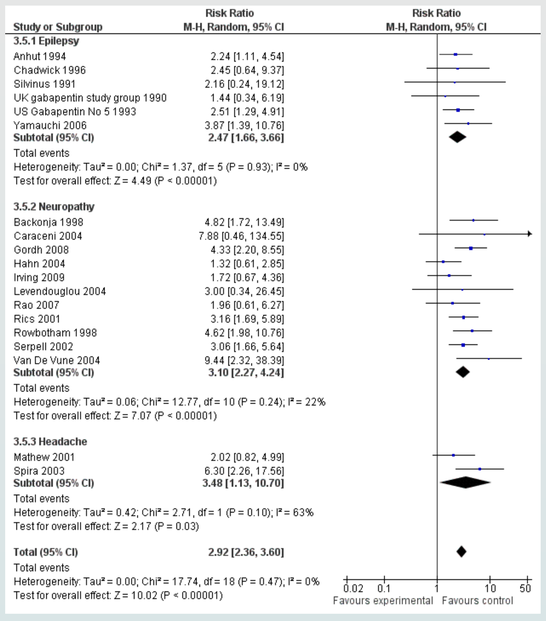


Fig 2. Forest plot of Relative Risk of Dizziness with Gabapentin, sub-grouped by indication. Data showing epilepsy, headache and neuropathy trials.

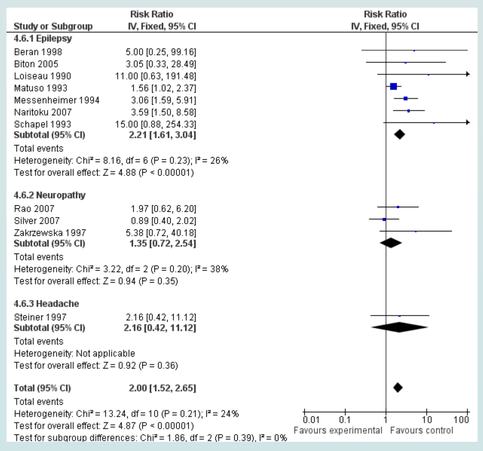


Fig 3. Forest plot of Relative Risk of Dizziness with Gabapentin, sub-grouped by indication. Data showing epilepsy, headache and neuropathy trials.

DIZZINESS	I^2 Test of Heterogeneity			
Indication / Intervention	Headache	Neuropathy	Epilepsy	Total when combine trials subgroups
Gabapentin	63%	22%	0%	0%
Lacosamide	na	0%	56%	19%
Topiramate	24%	0%	0%	0%
Oxcarbazepine	0%	na	8%	59%
Lamotrigine	na	38%	39%	0%

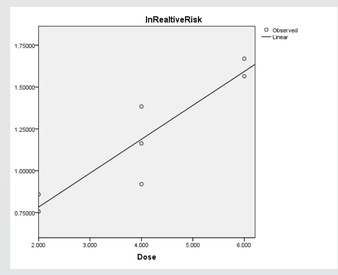
Table 1. Results of reduction in statistical heterogeneity when trails from other indications are pooled.

Outcome	Indication	Slope (dlnRR/dDose)	Intercept lnRR	Intercept RR
Ataxia	Epilepsy	0.176	0.984	2.67
Ataxia	Neuropathy	0.517	-0.543	0.58
Dizziness	Epilepsy	0.205	0.376	1.45
Dizziness	Neuropathy	0.364	-0.375	0.68
Fatigue	Epilepsy	0.202	0.376	1.45
Fatigue	Neuropathy	0.159	-0.375	0.68
Nausea	Epilepsy	0.002	1.054	2.87
Nausea	Neuropathy	0.170	-0.136	0.87
Somnolence	Epilepsy	0.159	-0.160	0.85
Somnolence	Neuropathy	-0.032	0.475	1.61

Table 2. Meta-regression when effect of dose is minimised of all outcomes for Lacosamide.

Outcome	Indication	Slope (dlnRR/dDose)	Intercept lnRR	Intercept RR
Ataxia	Epilepsy	No Data		
Ataxia	Neuropathy			
Dizziness	Epilepsy	0.017	0.626	1.87
Dizziness	Neuropathy	0.120	0.010	1.01
Fatigue	Epilepsy	0.015	0.545	1.72
Fatigue	Neuropathy	0.093	-0.750	0.47
Nausea	Epilepsy	0.031	0.550	1.73
Nausea	Neuropathy	0.136	-0.995	0.37
Somnolence	Epilepsy	0.048	0.298	1.35
Somnolence	Neuropathy	0.155	-1.281	0.28

Table 3. Meta-regression when effect of dose is minimised of all outcomes for Oxcarbazepine.



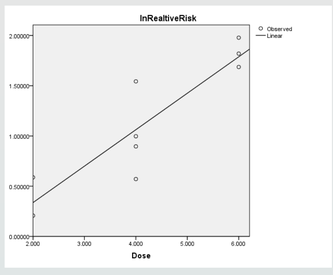


Fig4. Meta-regression curves for Lacosamide, (a) dizziness in epilepsy trials and (b) dizziness in neuropathy trials

RESULTS

- Our search revealed 106 eligible trial reports.
- Feasibility of using AE data from other indications varied by drug and outcome.
- We found that lacosamide showed the greatest feasibility. This was followed by topiramate, oxycarbazepine and lamotrigine.

Statistical Heterogeneity

- We show here the results for dizziness.
- Heterogeneity was reduced for three AEDs (lacosamide, gabapentin, topiramate and lamotrigine) but not for oxycarbazepine when dizziness is the outcome.

Meta-regression

- Calculated relative risks after the effect of dose was minimised showed a consistent higher risk in patients with epilepsy than those from other indications.
- Thus any statistical heterogeneity is accounted by patient factors which would be difficult to eliminate.

CONCLUSION

1. Adverse events across indications is a useful means of increasing power in meta-analysis.
2. Heterogeneity is a limiting factor in using trials from other indications in meta-analysis.
3. Heterogeneity is dependent on dose, outcome used and intervention.
4. Meta-regression methods to eliminate the effect of dose can not totally explain heterogeneity. This indicated that there are other factors that determine it.
5. We report that patients with epilepsy report a higher relative risk of adverse events than patients with other indications.
6. This could be explained by clinical differences between patients that impact on reporting of adverse events.

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